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DOI:
10.3310/hta23020

HEALTH TECHNOLOGY ASSESSMENT

VOLUME 23 ISSUE 2 JANUARY 2019
ISSN 1366-5278

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NHS
National Institute for Health Research

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Declared competing interests of authors: Susanna Esposito reports grants and personal fees from GlaxoSmithKline (GSK) plc (GSK House, Middlesex, UK), grants and personal fees from Pfizer Inc. (New York, NY, USA), grants and personal fees from Sanofi Pasteur MSD [Sanofi Pasteur (Lyon France) and Merck Sharp & Dohme Corp. (MSD, Kenilworth, NJ, USA)], grants from DuPage Medical Group (DMG, Downers Grove, IL, USA), personal fees from Valeas S.p.A. (Milan, Italy), and grants and personal fees from Vifor Pharma (Bern, Switzerland), outside the submitted work. Emma Goodall reports personal fees from GSK outside the submitted work. Wim Janssens reports grants from Instituut voor Innovatie door Wetenschap en Technologie (IWT)–Vlaanderen and from Laboratoires SMB (Brussels, Belgium) during the conduct of the study. David Mauger reports funding from the National Heart, Lung, and Blood Institute, MA, USA. Rachel Neale reports grants from the National Institutes of Health and the Medical Research Council during the conduct of the study. Judy R Rees reports that a use patent is held by Dartmouth College and Dr John A Baron for calcium as a chemopreventive agent. Dr Baron is not an author on this paper but is the principal investigator of the parent study from which the study by Rees (Rees JR, Hendricks K, Barry EL, Peacock JL, Mott LA, Sandler RS, *et al.* Vitamin D_3 supplementation and upper respiratory tract infections in a randomized, controlled trial. *Clin Infect Dis* 2013;**57**:1384–92) was conducted. The patent was previously licensed by Pfizer (with royalties), but has not been licensed for about 5 years. Judy R Rees is not involved in the patent and the patent does not involve vitamin D.

Published January 2019
DOI: 10.3310/hta23020

This report should be referenced as follows:

Martineau AR, Jolliffe DA, Greenberg L, Aloia JF, Bergman P, Dubnov-Raz G, *et al*. Vitamin D supplementation to prevent acute respiratory infections: individual participant data meta-analysis. *Health Technol Assess* 2019;**23**(2).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (SciSearch®) and *Current Contents®*/ Clinical Medicine.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.236

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the Clarivate Analytics Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 13/03/25. The contractual start date was in October 2014. The draft report began editorial review in January 2017 and was accepted for publication in October 2017. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care.

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Abstract

Vitamin D supplementation to prevent acute respiratory infections: individual participant data meta-analysis

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Background: Randomised controlled trials (RCTs) exploring the potential of vitamin D to prevent acute respiratory infections have yielded mixed results. Individual participant data (IPD) meta-analysis has the potential to identify factors that may explain this heterogeneity.

Objectives: To assess the overall effect of vitamin D supplementation on the risk of acute respiratory infections (ARIs) and to identify factors modifying this effect.

Data sources: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, ClinicalTrials.gov and the International Standard Randomised Controlled Trials Number (ISRCTN) registry.

Study selection: Randomised, double-blind, placebo-controlled trials of supplementation with vitamin D_3 or vitamin D_2 of any duration having incidence of acute respiratory infection as a prespecified efficacy outcome were selected.

Study appraisal: Study quality was assessed using the Cochrane Collaboration Risk of Bias tool to assess sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, completeness of outcome data, evidence of selective outcome reporting and other potential threats to validity.

Results: We identified 25 eligible RCTs (a total of 11,321 participants, aged from 0 to 95 years). IPD were obtained for 10,933 out of 11,321 (96.6%) participants. Vitamin D supplementation reduced the risk of ARI among all participants [adjusted odds ratio (aOR) 0.88, 95% confidence interval (CI) 0.81 to 0.96; heterogeneity $p < 0.001$]. Subgroup analysis revealed that protective effects were seen in individuals receiving daily or weekly vitamin D without additional bolus doses (aOR 0.81, 95% CI 0.72 to 0.91), but not in those receiving one or more bolus doses (aOR 0.97, 95% CI 0.86 to 1.10; $p = 0.05$). Among those receiving daily or weekly vitamin D, protective effects of vitamin D were stronger in individuals with a baseline 25-hydroxyvitamin D [25(OH)D] concentration of < 25 nmol/l (aOR 0.30, 95% CI 0.17 to 0.53) than in those with a baseline 25(OH)D concentration of ≥ 25 nmol/l (aOR 0.75, 95% CI 0.60 to 0.95; $p = 0.006$). Vitamin D did not influence the proportion of participants experiencing at least one serious adverse event (aOR 0.98, 95% CI 0.80 to 1.20; $p = 0.83$). The body of evidence contributing to these analyses was assessed as being of high quality.

Limitations: Our study had limited power to detect the effects of vitamin D supplementation on the risk of upper versus lower respiratory infection, analysed separately.

Conclusions: Vitamin D supplementation was safe, and it protected against ARIs overall. Very deficient individuals and those not receiving bolus doses experienced the benefit. Incorporation of additional IPD from ongoing trials in the field has the potential to increase statistical power for analyses of secondary outcomes.

Study registration: This study is registered as PROSPERO CRD42014013953.

Funding: The National Institute for Health Research Health Technology Assessment programme.

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25(OH)D	25-hydroxyvitamin D	IL	interleukin
aHR	adjusted hazard ratio	IPD	individual participant data
aIRR	adjusted incidence rate ratio	IU	international unit
aOR	adjusted odds ratio	LRI	lower respiratory infection
ARI	acute respiratory infection	NNT	number needed to treat
CI	confidence interval	PPI	patient and public involvement
COPD	chronic obstructive pulmonary disease	RCT	randomised controlled trial
GRADE	Grading of Recommendations Assessment, Development and Evaluation	URI	upper respiratory infection

Plain English summary

Research question

Does taking a vitamin D supplement help to prevent colds, flu and chest infections?

Background

Low blood levels of vitamin D (the 'sunshine vitamin') have been linked to an increased risk of colds, flu and chest infections, collectively termed 'acute respiratory infections' (ARIs). Clinical trials testing whether or not vitamin D supplements can prevent ARIs have had mixed results. The reason why vitamin D appears to work in some situations but not others is not understood. In order to answer this question, we obtained data from individuals who took part in previous clinical trials, combined them and analysed them to answer two questions:

1. Does vitamin D reduce the overall risk of ARIs, broadly defined?
2. Do some people benefit more from taking vitamin D than others?

Included studies

We obtained raw data on a total of 10,933 people from 25 trials conducted in 15 countries. Participants were aged from 0 to 95 years. All of the studies compared vitamin D with placebo (dummy medication), which is the gold standard trial design.

Key results

Overall, vitamin D supplements reduced the risk of having at least one ARI from 42% to 39%. We also showed that vitamin D had greater protective effects when it was given daily or weekly to people with the lowest vitamin D levels: the risk of having at least one ARI was reduced from 60% to 32% in these individuals. Vitamin D was not effective in protecting against ARIs when it was given in large, widely spaced doses. Taking vitamin D supplements was found to be safe.

Conclusion

Taking a vitamin D supplement can protect against ARIs. The strongest effects are seen when a daily or weekly supplement is given to people with the lowest vitamin D levels.

Scientific summary

Background

Acute respiratory infections (ARIs) are a major cause of global morbidity and mortality. Observational studies report consistent independent associations between low serum concentrations of 25-hydroxyvitamin D [25(OH)D], the major circulating vitamin D metabolite, and susceptibility to ARI. The observation that 25(OH)D supports induction of antimicrobial peptides in response to both viral and bacterial stimuli suggests a potential mechanism by which vitamin D-inducible protection against these outcomes may be mediated. Vitamin D metabolites have also been reported to induce other innate antimicrobial effector mechanisms, including autophagy and synthesis of reactive nitrogen intermediates and reactive oxygen intermediates.

These epidemiological and in vitro data have prompted numerous randomised controlled trials (RCTs) to determine whether or not vitamin D supplementation can decrease the risk of ARI. A total of five aggregate data meta-analyses incorporating data from up to 15 primary trials have been conducted to date, of which two report statistically significant protective effects and three report no statistically significant effects. All but one of these aggregate data meta-analyses reported significant heterogeneity of effect between primary trials.

Such heterogeneity of effect may have arisen as a result of intertrial variation in participant characteristics and in dosing regimens, either of which may modify the effects of vitamin D supplementation on immunity to respiratory pathogens. Subgroup analyses within primary trials of vitamin D supplementation for diverse indications show that participants with lower baseline vitamin D status may derive greater clinical benefit from supplementation than those with higher baseline status. Administration of large boluses of vitamin D has been associated with reduced efficacy for non-classical effects of vitamin D and, in some cases, increased risk of adverse outcomes. Although study-level factors are amenable to exploration via aggregate data meta-analysis of published data, potential effect modifiers operating at an individual level, such as baseline vitamin D status, can only be explored using individual participant data (IPD) meta-analysis. This is because subgroups are not consistently disaggregated in trial reports, and consistent adjustments for potential confounders cannot be applied. In order to determine the overall effect of vitamin D supplementation on the risk of ARI and to identify factors that might modify the effects of this intervention on the risk of ARI, we undertook a meta-analysis of IPD from RCTs that had investigated these outcomes.

Main objectives

1. To determine the overall effect of vitamin D supplementation on the risk of ARI and serious adverse events.
2. To determine whether or not the following factors modify the effect of vitamin D supplementation on the risk of ARI:

    i. baseline vitamin D status
    ii. vitamin D dosing regimen
    iii. size of vitamin D dose
    iv. age
    v. body mass index
    vi. presence versus absence of respiratory comorbidity [e.g. asthma, chronic obstructive pulmonary disease (COPD)]
    vii. influenza vaccination status.

Methods

Data sources

Two investigators searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, ClinicalTrials.gov and the International Standard Randomised Controlled Trials Number (ISRCTN) registry for eligible studies from database inception until December 2015.

Study selection (eligibility criteria)

Randomised, double-blind, placebo-controlled trials of supplementation with vitamin D_3 or vitamin D_2 of any duration were eligible for inclusion in the ARI analysis if they had been approved by a Research Ethics Committee and if data on incidence of ARI were collected prospectively and prespecified as an efficacy outcome. Studies reporting results of long-term follow-up of primary RCTs were excluded.

Data management

Individual participant data were requested from the principal investigator for each eligible trial, and the terms of collaboration were specified in a data transfer agreement, signed by representatives of the data provider and the recipient (Queen Mary University of London). Data relating to study characteristics were extracted for the following variables: setting, eligibility criteria, details of intervention and control regimens, study duration and case definitions for ARI. IPD were extracted for the following variables, when available: baseline data were requested for age, sex, cluster identification (cluster randomised trials only), influenza vaccination status, history of asthma, history of COPD, weight, height (adults and children able to stand) or length (infants), serum 25(OH)D concentration, study allocation (vitamin D vs. placebo) and details of any stratification or minimisation variables. Follow-up data were requested for the total number of ARIs, upper respiratory infections (URIs) and lower respiratory infections (LRIs) experienced during the trial, time from first dose of study medication to first ARI/URI/LRI if applicable, total number of courses of antibiotics taken for ARI during the trial, total number of days off work or school as a result of ARI symptoms during the trial, serum 25(OH)D concentration at final follow-up, duration of follow-up, number and nature of serious adverse events, number of adverse reactions (incident hypercalcaemia or renal stones) and end-trial status (completed vs. withdrew vs. lost to follow-up vs. died).

Data were de-identified at source prior to transfer via e-mail. On receipt, three investigators assessed data integrity by performing internal consistency checks and by attempting to replicate the results of the analysis for ARI incidence when this was published in the trial report. Study authors were contacted to provide missing data and to resolve queries arising from these integrity checks. Once queries had been resolved, clean data were uploaded to the main study database.

Assessment of validity

The Cochrane Collaboration Risk of Bias tool was used to assess the following variables: sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; completeness of outcome data; evidence of selective outcome reporting; and other potential threats to validity.

Data synthesis

Initially, all studies were reanalysed separately; the original authors were asked to confirm the accuracy of this reanalysis when it had been performed previously, and any discrepancies were resolved. Then we performed both one-step and two-step IPD meta-analysis using a random-effects model adjusted for age, sex and study duration to obtain the pooled intervention effect on (1) the proportion of participants experiencing at least one ARI, (2) ARI rate and (3) time to first ARI with a 95% confidence interval (CI). The number needed to treat (NNT) for an additional beneficial outcome was calculated in which meta-analysis of dichotomous outcomes revealed a statistically significant beneficial effect of allocation to vitamin D compared with placebo.

In order to explore the causes of heterogeneity and identify factors modifying the effects of vitamin D supplementation on ARI risk, we also performed prespecified subgroup analyses by extending the one-step meta-analysis framework to include treatment–covariate interaction terms. Subgroups were defined

according to baseline vitamin D status [serum 25(OH)D concentration of < 25 nmol/l vs. ≥ 25 nmol/l], vitamin D dosing regimen [daily or weekly administration without bolus dosing vs. administration of a regimen including at least one bolus dose of ≥ 30,000 IU (international units) of vitamin D], dose size (daily equivalent < 800 IU vs. 800–1999 IU vs. ≥ 2000 IU), age (≤ 1 year vs. 1.1–15.9 years vs. 16–65 years vs. > 65 years), body mass index (< 25 kg/m^2 vs. ≥ 25 kg/m^2) and presence versus absence of asthma, COPD and previous influenza vaccination. Interaction analyses were adjusted for potential confounders (age, sex and study duration) in order to ensure that reported subgroup effects were independent. In order to minimise the chance of type I error arising from multiple analyses, significance was inferred only when *p*-values for treatment–covariate interaction terms were < 0.05.

Results

We identified 25 RCTs (total 11,321 participants, aged from 0 to 95 years) that were eligible for the ARI analysis. These trials were conducted in 15 different countries on four continents and enrolled participants of both sexes from birth to 95 years of age. The mean baseline 25(OH)D concentration ranged from 18.9 to 88.9 nmol/l. All studies administered oral vitamin D_3 to participants in the intervention arm: this was given as monthly to once every 3 months bolus doses in seven studies, as weekly doses in three studies, as a daily dose in 12 studies and as a combination of bolus and daily doses in three studies. Study duration ranged from 7 weeks to 1.5 years. Incidence of ARI was a primary or coprimary outcome for 14 studies and a secondary outcome for 11 studies.

Individual participant data were obtained for 10,933 out of 11,321 (96.6%) participants in these studies. In the one-step IPD meta-analysis, vitamin D supplementation resulted in a statistically significant reduction in the proportion of participants experiencing at least one ARI [adjusted Odds Ratio (aOR) 0.88, 95% CI 0.81 to 0.96; $p = 0.003$, p for heterogeneity < 0.001; 10,933 participants in 25 studies]. The number needed to benefit was 33 (95% CI 20 to 101). Statistically significant protective effects of vitamin D were also seen for one-step analyses of ARI rate [adjusted incidence rate ratio (aIRR) 0.96, 95% CI 0.92 to 0.997; $p = 0.04$; p for heterogeneity < 0.001; 10,703 participants in 25 studies] but not for analysis of time to first ARI [adjusted hazard ratio (aHR) 0.95, 95% CI 0.89 to 1.01; $p = 0.09$; p for heterogeneity < 0.001; 9108 participants in 18 studies]. Two-step analyses showed consistent effects for the proportion of participants experiencing at least one ARI (aOR 0.80, 95% CI 0.69 to 0.93; $p = 0.004$; p for heterogeneity = 0.001; 10,899 participants in 24 studies), ARI rate (aIRR 0.91, 95% CI 0.84 to 0.98; $p = 0.018$; p for heterogeneity < 0.001; 10,703 participants in 25 studies) and time to first ARI (aHR 0.92, 95% CI 0.85 to 1.00; $p = 0.051$; p for heterogeneity = 0.14; 9108 participants in 18 studies). Vitamin D did not influence the proportion of participants experiencing at least one serious adverse event (aOR 0.98, 95% CI 0.80 to 1.20; $p = 0.83$). This evidence was assessed as being of high quality.

Subgroup analyses revealed a strong protective effect of vitamin D supplementation among individuals with baseline circulating 25(OH)D concentration of < 25 nmol/l (aOR 0.58, 95% CI 0.40 to 0.82; NNT 8, 95% CI 5 to 21; 538 participants in 14 studies; within subgroup, $p = 0.002$), and no statistically significant effect among those with baseline 25(OH)D concentration of ≥ 25 nmol/l (aOR 0.89, 95% CI 0.77 to 1.04; 3634 participants in 19 studies; within subgroup, $p = 0.15$; for interaction, $p = 0.01$). Stronger protective effects of vitamin D against ARIs were also seen in trials in which vitamin D was administered using a daily or weekly regimen without additional bolus doses (aOR 0.81, 95% CI 0.72 to 0.91; NNT 20, 95% CI 13 to 43; 5133 participants in 15 studies; within subgroup, $p < 0.001$); no such protective effect was seen among participants in trials in which at least one bolus dose of vitamin D was administered (aOR 0.97, 95% CI 0.86 to 1.10; 5800 participants in 10 studies; within subgroup, $p = 0.67$; p for interaction = 0.05). For both of these subgroup analyses, broadly consistent effects were observed for event rate analysis and survival analysis. The *p*-values for interaction were > 0.05 for all other potential effect modifiers investigated.

We then proceeded to stratify the subgroup analyses according to dosing frequency, in order to provide a cleaner look at results of subgroup analyses under the assumption that administration of bolus doses was ineffective.The results of this exploratory analysis suggested that daily or weekly administration of vitamin D induced an even greater degree of protection against ARI among participants with baseline circulating 25(OH)D concentrations of < 25 nmol/l than in the unstratified analysis (aOR 0.30, 95% CI 0.17 to 0.53; NNT 4, 95% CI 3 to 7; 234 participants in six studies; within subgroup, $p < 0.001$). Moreover, administration of daily or weekly vitamin D also protected against ARI among participants with higher baseline 25(OH)D concentrations (aOR 0.75, 95% CI 0.60 to 0.95; NNT 15, 95% CI 9 to 86; 1603 participants in six studies; within subgroup, $p = 0.02$). The *p*-value for interaction for this subgroup analysis was 0.006, indicating that protective effects of daily or weekly vitamin D supplementation were significantly greater in the subgroup of participants with profound vitamin D deficiency. No other statistically significant interaction was seen; notably, bolus dose vitamin D supplementation did not offer any protection against ARI even when administered to those with circulating 25(OH)D concentrations of < 25 nmol/l (aOR 0.82, 95% CI 0.51 to 1.33; 304 participants in eight studies; within subgroup, $p = 0.43$).

Limitations

Our power to detect effects of vitamin D supplementation was limited for some subgroups [e.g. individuals with baseline 25(OH)D concentration of < 25 nmol/l receiving bolus-dosing regimens]. Null and borderline significant results for analyses of these outcomes may have arisen as a consequence of type II error. Data relating to adherence to study medication were not available for all subjects. However, the inclusion of non-adherent participants would bias results of our intention-to-treat analysis towards the null; thus, we conclude that effects of vitamin D in those who are fully adherent to supplementation will be no less than those reported for the study population overall. Finally, we caution that study definitions of ARI were diverse, and virological, microbiological and/or radiological confirmation was obtained for a minority of events. ARI is often a clinical diagnosis in practice, however, and as all studies were double-blind and placebo-controlled, differences in incidence of events between study arms cannot be attributed to observation bias.

Conclusions

Implications for health care

Our synthesis of the current evidence suggests that vitamin D supplementation can prevent ARIs, broadly defined. We identified that the greatest potential benefit is for those individuals who are very deficient in vitamin D. Those receiving daily or weekly supplementation without additional bolus doses also experienced particular benefit. Our results add to the body of evidence supporting the introduction of public health measures, such as food fortification, to improve vitamin D status in settings in which profound vitamin D deficiency is common.

Recommendations for research

1. Incorporation of additional IPD from ongoing trials in the field has the potential to increase statistical power for subgroup analyses; this IPD meta-analysis should therefore be updated when a significant new body of data has accumulated.
2. Given the major impact of ARIs on economic productivity and health-care use, our findings are likely to influence the economic case for the introduction of vitamin D fortification of foods in the UK. Economic models of the cost-effectiveness of vitamin D fortification in the UK should therefore be updated to take account of the previously unappreciated protective effects of vitamin D against ARIs.

Study registration

This study is registered as PROSPERO CRD42014013953.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Background

Acute respiratory infections (ARIs) are a major cause of global morbidity and mortality, responsible for 10% of ambulatory and emergency department visits in the USA[1] and an estimated 2.65 million deaths worldwide in 2013.[2] Viral ARI precipitate the majority of acute exacerbations of asthma and chronic obstructive pulmonary disease (COPD),[3] which represent the major cause of morbidity and mortality in people with these conditions.[4,5]

Observational studies report consistent independent associations between low serum concentrations of 25-hydroxyvitamin D [25(OH)D], the major circulating vitamin D metabolite, and susceptibility to ARI[6,7] and acute exacerbations of asthma;[8,9] such observational studies have yielded more conflicting results for the outcomes of COPD exacerbation.[10–12] The observation that 25(OH)D supports induction of antimicrobial peptides in response to both viral and bacterial stimuli[13–15] suggests a potential mechanism by which vitamin D-inducible protection against these outcomes may be mediated. Vitamin D metabolites have also been reported to induce other innate antimicrobial effector mechanisms, including autophagy and synthesis of reactive nitrogen intermediates and reactive oxygen intermediates.[16] In addition, vitamin D metabolites have been reported to induce anti-inflammatory activity via multiple mechanisms, including induction of the regulatory cytokine interleukin (IL) 10[17] and inhibition of the pro-inflammatory cytokine IL-17A.[18] We have also recently shown that 25(OH)D attenuates rhinovirus-induced expression of the genes encoding intercellular adhesion molecule 1 (ICAM-1, a cell surface glycoprotein that acts as the cellular receptor for major group rhinoviruses) and platelet-activating factor receptor (PAFR, a G-protein coupled receptor implicated in adhesion of *Streptococcus pneumoniae* to respiratory epithelial cells).[19] These findings suggest possible mechanisms by which vitamin D may enhance resistance to rhinovirus infection and reduce risk of secondary bacterial infection in vitamin D-deficient individuals.

These epidemiological and in vitro data have prompted numerous randomised controlled trials (RCTs) to determine whether or not vitamin D supplementation can decrease the risk of ARI and acute exacerbations of asthma and COPD. For the outcome of ARI, a total of five aggregate data meta-analyses incorporating data from up to 15 primary trials have been conducted to date, of which two report statistically significant protective effects[20,21] and three report no statistically significant effects.[22–24] All but one of these aggregate data meta-analyses[22] reported significant heterogeneity of effect between primary trials. For the outcome of asthma exacerbation, a total of four aggregate data meta-analyses incorporating data from up to nine primary trials have been conducted to date, of which three report statistically significant protective effects[23,25,26] and one reports no statistically significant effects.[27] The most recent of these – and the one incorporating data from the most studies – reported a high degree of heterogeneity of effect between trials for the outcome of study-defined asthma exacerbation.[26] We are not aware of any published meta-analyses investigating effects of vitamin D supplementation on the risk of COPD exacerbation, which may reflect the fact that only three primary trials investigating this question have been published to date.[28–30]

When heterogeneity of effect is present, it may have arisen as a result of intertrial variation in participant characteristics and in dosing regimens, either of which may modify the effects of vitamin D supplementation on immunity to respiratory pathogens.[31] Subgroup analyses within primary trials suggest that COPD patients with lower baseline vitamin D status may derive greater clinical benefit from supplementation than those with higher baseline status.[28,29] Moreover, participant characteristics such as age and body mass index have been reported to modify the 25(OH)D response to vitamin D supplementation.[32,33] Administration of large boluses of vitamin D has been associated with reduced efficacy for non-classical effects[20] and, in some cases, increased risk of adverse outcomes.[34] Although study-level factors are amenable to exploration via aggregate data meta-analysis of published data, potential effect modifiers operating at an individual level, such as baseline vitamin D status, can only be explored using individual participant data (IPD) meta-analysis.

This is because subgroups are not consistently disaggregated in trial reports, and consistent adjustments for potential confounders cannot be applied.[35] In order to identify factors that might modify effects of vitamin D supplementation on the risk of ARI and acute exacerbations of asthma and COPD, we undertook a meta-analysis of IPD from RCTs that had investigated these outcomes. The results of some of these analyses have been published elsewhere.[36–38]

Chapter 2 Research questions

1. What is the overall effect of vitamin D supplementation on the risk of:

    i. acute respiratory infections, incorporating events classified as upper respiratory infections (URIs), lower respiratory infections (LRIs) and ARIs of unclassified location (i.e. infection of the upper and/or lower respiratory tract)
    ii. upper respiratory infections and LRIs, analysed separately
    iii. emergency department attendance and/or hospital admission for ARI
    iv. use of antimicrobials for treatment of ARI
    v. work/school absence as a result of ARI
    vi. severe exacerbations of asthma
    vii. severe exacerbations of COPD
    viii. serious adverse events
    ix. potential adverse reactions to vitamin D (hypercalcaemia and renal stones)
    x. mortality (related to ARI/respiratory failure, infection and all-cause) and to identify factors modifying this effect?

2. Do the following factors modify the effect of vitamin D supplementation on the risk of ARI?

    i. baseline vitamin D status [serum 25(OH)D concentration of < 25 nmol/l vs. ≥ 25 nmol/l]
    ii. dosing regimen [daily or weekly administration of vitamin D without bolus dosing vs. administration of a regimen including at least one bolus dose of $\geq 30{,}000$ international units (IU) of vitamin D]
    iii. dose size (daily equivalent < 800 IU vs. 800–1999 IU vs. ≥ 2000 IU of vitamin D)
    iv. age (≤ 1 year vs. 1.1–15.9 years vs. 16–65 years vs. > 65 years)
    v. body mass index (< 25 kg/m^2 vs. ≥ 25 kg/m^2)
    vi. presence versus absence of respiratory comorbidity (asthma, COPD)
    vii. influenza vaccination status.

Chapter 3 Methods

Protocol and registration

Methods were prespecified in a protocol that was registered with the PROSPERO International Prospective Register of Systematic Reviews [www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014013953 accessed 1 May 2018]. Research Ethics Committee approval to conduct this meta-analysis was not required in the UK; local ethics permission to contribute de-identified IPD from primary trials was required and obtained for studies by Camargo *et al.*[39] (the Ethics Review Committee of the Mongolian Ministry of Health), Murdoch *et al.*[40] (Southern Health and Disability Ethics Committee, reference URB/09/10/050/AM02), Rees *et al.*[41] (Committee for the Protection of Human Subjects, Dartmouth College, NH, USA; Protocol no 24381), Tachimoto *et al.*[42] (Ethics Committee of the Jikei University School of Medicine, reference 26-333: 7839), Tran *et al.*[43] (QIMR Berghofer Medical Research Institute Human Research Ethics Committee, reference number P1570) and Urashima *et al.*[44,45] (Ethics Committee of the Jikei University School of Medicine, reference 26-333: 7839).

Patient and public involvement

Two patient and public involvement (PPI) representatives were involved in development of the research question and the choice of outcome measures specified in the study protocol through discussion with the investigators. When possible, results of this systematic review and meta-analysis will be disseminated to individual participants via the principal investigators of each trial (e.g. via e-mail to participants who have requested updates on how their data are being used). PPI representatives and participants in primary trials are thanked for their contributions in the *Acknowledgements*.

Eligibility criteria

For the IPD meta-analysis of ARI outcomes, randomised, double-blind, placebo-controlled trials of supplementation with vitamin D_3 or vitamin D_2 of any duration were eligible for inclusion if they had been approved by a Research Ethics Committee and if data on incidence of ARI were collected prospectively and prespecified as an efficacy outcome. The last requirement was imposed to minimise misclassification bias (prospectively designed instruments to capture these events were deemed more likely to be sensitive and specific for this outcome). Studies reporting results of long-term follow-up of primary RCTs were excluded.

For the IPD meta-analysis of asthma exacerbation, randomised, double-blind, placebo-controlled trials of supplementation with vitamin D_3 or vitamin D_2 in patients with asthma were eligible for inclusion if they had been approved by a Research Ethics Committee and if data on incidence of asthma exacerbation were reported.

For the IPD meta-analysis of COPD exacerbation, randomised, double-blind, placebo-controlled trials of supplementation with vitamin D_3 or vitamin D_2 in patients with COPD were eligible for inclusion if they had been approved by a Research Ethics Committee and if data on incidence of COPD exacerbation were reported.

Study identification and selection

Two investigators (ARM and DAJ) searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, ClinicalTrials.gov and the International Standard Randomised Controlled Trials Number (ISRCTN) registry using the electronic search strategies described in *Appendix 1*. Searches were regularly updated up to and including 31 December 2015 for the ARI analysis, 26 October 2016 for the analysis of asthma exacerbations and 31 July 2017 for the analysis of COPD exacerbations. No language restrictions were imposed. These searches were supplemented by searching review articles and reference lists of trial publications. Collaborators were asked if they knew of any additional trials. Three investigators (ARM, CAC and DAJ) determined which trials met the eligibility criteria; disagreements were resolved by consensus. References were managed in EndNote X5 [Clarivate Analytics (formerly Thomson Reuters), Philadelphia, PA, USA].

Data collection processes

Individual participant data were requested from the principal investigator for each eligible trial and the terms of collaboration were specified in a data transfer agreement, signed by representatives of the data provider and the recipient (Queen Mary University of London). Data were de-identified at source prior to transfer via e-mail. On receipt, three investigators (DAJ, RLH and LG) assessed data integrity by performing internal consistency checks and by attempting to replicate results of analyses that were published in trial reports. Study authors were contacted to provide missing data and to resolve queries arising from these integrity checks. Once queries had been resolved, clean data were uploaded to the main study database, which was held in Stata® IC version12 (StataCorp LP, College Station, TX, USA).

Data relating to study characteristics were extracted for the following variables: setting, eligibility criteria, details of intervention and control regimens, study duration and case definitions for ARI. IPD were extracted for the following variables, when available: baseline data were requested for age, sex, cluster ID (cluster randomised trials only), racial/ethnic origin, influenza vaccination status, history of asthma, history of COPD, weight, height (adults and children able to stand) or length (infants), serum 25(OH)D concentration, study allocation (vitamin D vs. placebo) and details of any stratification or minimisation variables. For all trials, follow-up data were requested for serum 25(OH)D concentration at final follow-up, duration of follow-up, number and nature of serious adverse events, number of adverse reactions (incident hypercalcaemia or renal stones) and end-trial status (completed vs. withdrew vs. lost to follow-up vs. died). For trials contributing IPD to the ARI analysis, follow-up data were also requested for the total number of ARIs, URIs and LRIs experienced during the trial, time from first dose of study medication to first ARI/URI/LRI if applicable, total number of courses of antibiotics taken for ARI during the trial and total number of days off work or school as a result of ARI symptoms during the trial. For trials contributing IPD to the analysis of severe asthma exacerbation, follow-up data were also requested for the total number of asthma exacerbations experienced during the trial that were treated with systemic corticosteroids and the time from the first dose of study medication to the first such exacerbation, if applicable. For trials contributing IPD to the analysis of severe COPD exacerbation, follow-up data were also requested for the total number of COPD exacerbations experienced during the trial that were treated with systemic corticosteroids and/or antibiotics and the time from the first dose of study medication to the first such exacerbation if applicable.

Risk-of-bias assessment for individual studies

We used the Cochrane Collaboration Risk of Bias tool[46] to assess the following variables: sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; completeness of outcome data; evidence of selective outcome reporting; and other potential threats to validity. Study quality was assessed independently by two investigators (ARM and DAJ), except for the three trials by Martineau *et al.*,[29,47,48] which were assessed by Carlos A Camargo Jr. Discrepancies were resolved by consensus.

Definition of outcomes

The primary outcome of the meta-analysis was incidence of ARI, incorporating events classified as URIs, LRIs and ARIs of unclassified location (i.e. infection of the upper and/or lower respiratory tract). Secondary outcomes were incidence of URI and LRI, analysed separately; incidence of emergency department attendance and/or hospital admission for ARI; use of antimicrobials for treatment of ARI; work/school absence as a result of ARI; incidence of severe asthma exacerbation, defined as a worsening of asthma symptoms resulting in treatment with systemic corticosteroids; incidence of severe COPD exacerbation, defined as a worsening of symptoms resulting in treatment with systemic corticosteroids and/or antibiotics; incidence and nature of serious adverse events; incidence of potential adverse reactions to vitamin D (hypercalcaemia and renal stones); and mortality (related to ARI/respiratory failure, infection and all-cause).

Synthesis methods

Data were analysed by Lauren Greenberg and Richard L Hooper. Our IPD meta-analysis approach followed published guidelines.[35] Initially, all studies were reanalysed separately; the original authors were asked to confirm the accuracy of this reanalysis when it had been performed previously, and any discrepancies were resolved. We then performed both one-step and two-step IPD meta-analysis using a random-effects model adjusted for age, sex and study duration to obtain the pooled intervention effect with a 95% confidence interval (CI). We did not adjust for other covariates because missing values for some participants would have led to their exclusion from statistical analyses. In the one-step approach, IPD from all studies were modelled simultaneously while accounting for the clustering of participants within studies. In the two-step approach, IPD were first analysed for each separate study independently to produce an estimate of the treatment effect for that study; these data were then synthesised in a second step.[35] For one-step IPD meta-analysis, heterogeneity was assessed by calculation of the standard deviation of random effects; for two-step IPD meta-analysis, heterogeneity was summarised using the I^2 statistic. The number needed to treat (NNT) for an additional beneficial outcome was calculated using the Visual Rx NNT calculator (www.nntonline.net/visualrx/) when meta-analysis of dichotomous outcomes revealed a statistically significant beneficial effect of allocation to vitamin D versus placebo.

Exploration of variation in effects

In order to explore the causes of heterogeneity and identify factors modifying the effects of vitamin D supplementation on ARI risk, we performed prespecified subgroup analyses by extending the one-step meta-analysis framework to include treatment–covariate interaction terms. Subgroups were defined according to baseline vitamin D status [serum 25(OH)D concentration of < 25 nmol/l vs. ≥ 25 nmol/l], vitamin D dosing regimen (daily or weekly administration without bolus dosing vs. administration of a regimen including at least one bolus dose of $\geq 30{,}000$ IU of vitamin D), dose size (daily equivalent < 800 IU vs. 800–1999 IU vs. ≥ 2000 IU), age (≤ 1 year vs. 1.1–15.9 years vs. 16–65 years vs. > 65 years), body mass index (< 25 kg/m^2 vs. ≥ 25 kg/m^2), presence versus absence of asthma or COPD and previous influenza vaccination status. Interaction analyses were adjusted for potential confounders (age, sex and study duration) to ensure that reported subgroup effects were independent. The 25 nmol/l cut-off point for baseline 25(OH)D concentration in subgroup analyses was selected on the basis that it is the threshold for vitamin D deficiency defined by the UK Department of Health and Social Care[49] and the level below which participants in clinical trials have experienced the most consistent benefits of supplementation.[50] In order to minimise the chance of type I error arising from multiple analyses, significance was inferred only when p-values for treatment–covariate interaction terms were < 0.05.

Quality assessment across studies

For the primary analysis, the likelihood of publication bias was investigated through the construction of a contour-enhanced funnel plot.[51] We used the five Grading of Recommendations Assessment, Development and Evaluation (GRADE) considerations [(1) (study limitations, (2) consistency of effect, (3) imprecision, (4) indirectness and (5) publication bias][52] to assess the quality of the body of evidence contributing to analyses of the primary efficacy outcome and major safety outcome of our meta-analysis.

Additional analyses

For the ARI analysis, we conducted sensitivity analyses excluding IPD from trials in which ARI was a secondary outcome (as opposed to a primary or coprimary outcome) and in which risk of bias was assessed as being unclear. We also conducted a responder analysis in participants randomised to the intervention arm of included studies for whom end-study 25(OH)D concentration data were available, comparing risk of ARI in those who attained a serum concentration of 25(OH)D of $\geq$ 75 nmol/l with that in those who did not.

Chapter 4 Results

Study selection and individual participant data obtained

For the ARI analysis, our search identified a total of 532 unique studies that were assessed for eligibility; of these, 25 studies with a total of 11,321 randomised participants fulfilled eligibility criteria. IPD were sought and obtained for all 25 studies. Outcome data were obtained for 10,933 out of 11,321 (96.6%) of the randomised participants in these 25 studies (*Figure 1*).

For the analysis of severe asthma exacerbations, our search identified a total of 483 unique studies that were assessed for eligibility; of these, eight studies with a total of 1078 randomised participants fulfilled eligibility criteria. IPD were obtained for seven of the eight studies. Outcome data were obtained for 955 out of 978 (97.6%) of the randomised participants in these seven studies (*Figure 2*).

For the analysis of severe COPD exacerbations, our search identified a total of 254 unique studies that were assessed for eligibility; of these, three studies with a total of 510 randomised participants fulfilled eligibility criteria. IPD were obtained for two of the three studies. Outcome data were obtained for 422 out of 422 (100%) of the randomised participants in these two studies (*Figure 3*).

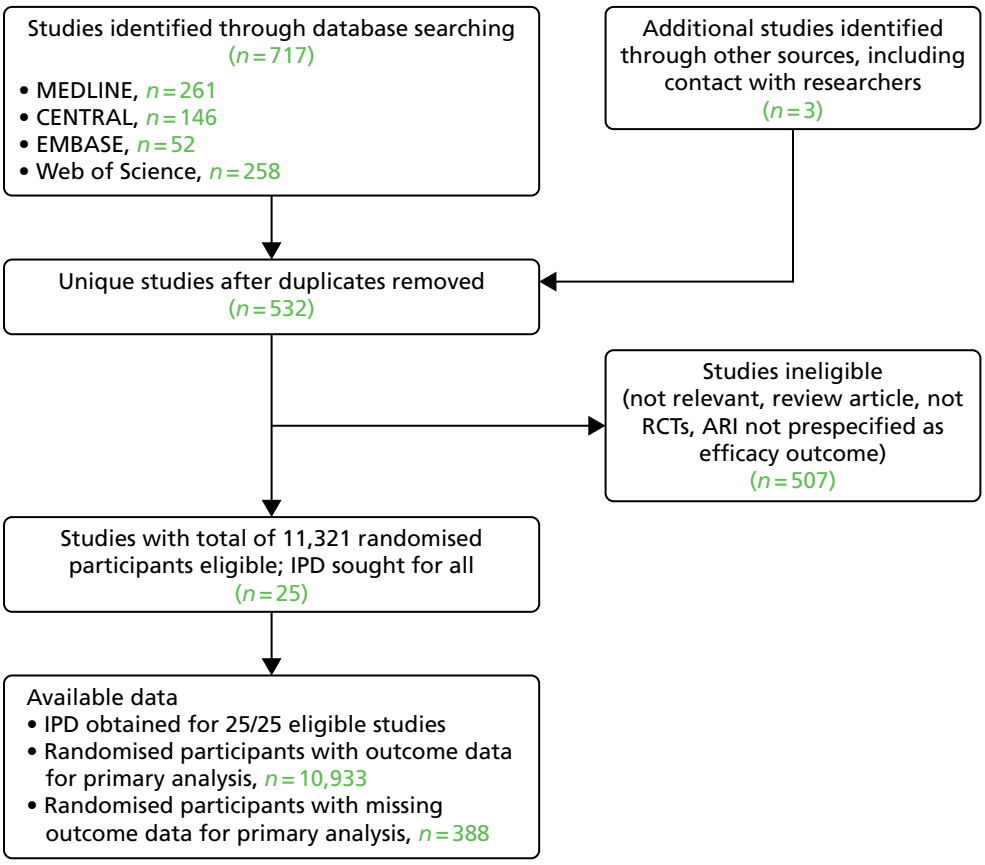

FIGURE 1 The PRISMA flow diagram: ARI analysis. CENTRAL, Cochrane Central Register of Controlled Trials; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

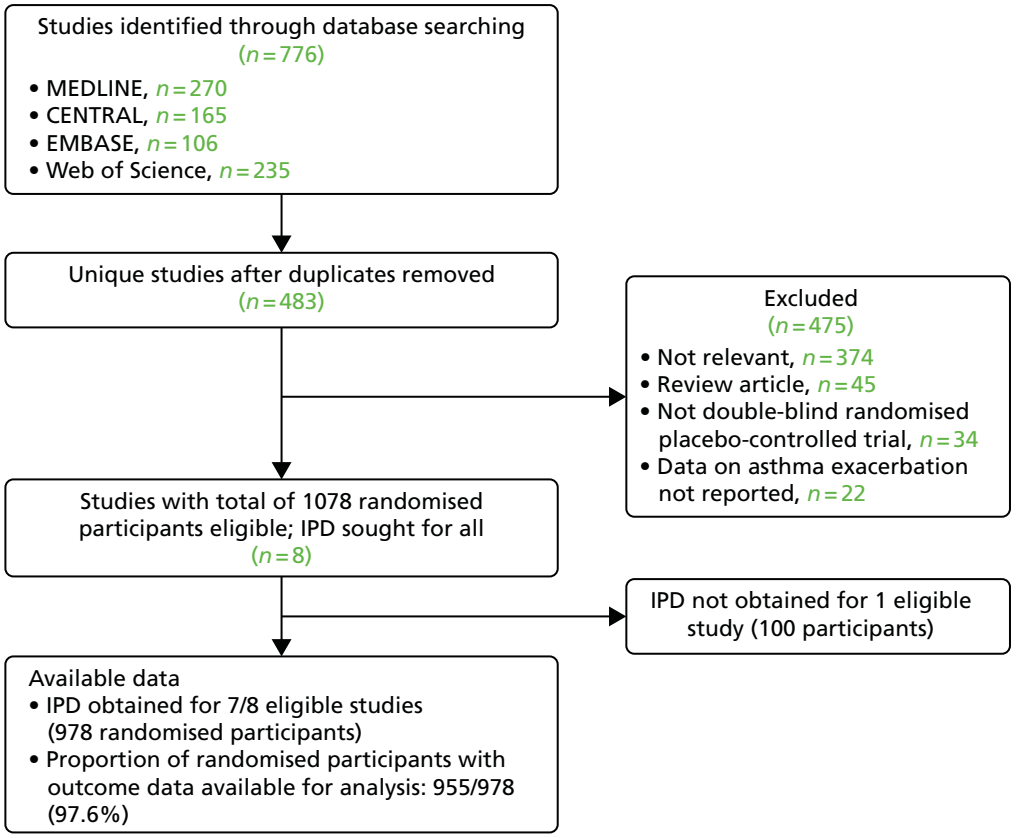

FIGURE 2 The PRISMA flow diagram: asthma exacerbation analysis. CENTRAL, Cochrane Central Register of Controlled Trials; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

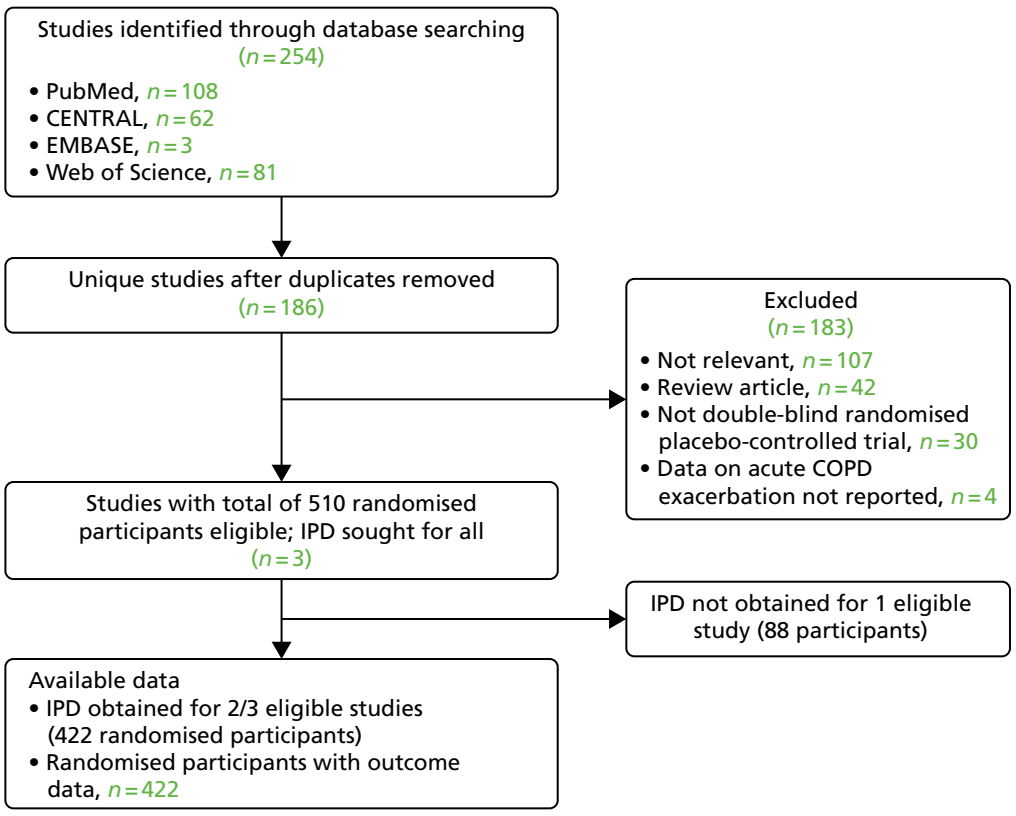

FIGURE 3 The PRISMA flow diagram: COPD exacerbation analysis. CENTRAL, Cochrane Central Register of Controlled Trials; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Study and participant characteristics

Characteristics of studies contributing data to this meta-analysis and their participants are presented in *Table 1*.

Trials were conducted in 15 different countries on four continents and enrolled participants of both sexes from birth to 95 years of age. Baseline serum 25(OH)D concentrations were determined in 21 out of 27 trials: the mean baseline 25(OH)D concentration ranged from 18.9 to 88.9 nmol/l. All studies administered oral vitamin D_3 to participants in the intervention arm: this was given as monthly to once every 3 months bolus doses in seven studies, as weekly doses in three studies, as a daily dose in 13 studies, and as a combination of bolus and daily doses in four studies. Study duration ranged from 7 weeks to 1.5 years. Incidence of ARI was a primary or coprimary outcome for 14 studies, and a secondary outcome for 11 studies. Incidence of asthma exacerbation was a primary or coprimary outcome for two studies and a secondary outcome for five studies. Incidence of COPD exacerbation was a primary or coprimary outcome for two studies; no study included this as a secondary outcome.

The integrity of the IPD was confirmed by replication of the primary analyses in published papers when applicable. The process of checking IPD identified three minor errors in published reports. For the 2012 trial by Manaseki-Holland *et al.*,[58] the correct number of repeat episodes of chest radiograph-confirmed pneumonia was 134, rather than 138 as reported. For the trial by Dubnov-Raz *et al.*,[64] the number of patients randomised to the intervention arm was 27, rather than 28 as reported. For the trial by Laaksi *et al.*,[55] the proportion of men randomised to placebo who did not experience any ARI was 30 out of 84, rather than 30 out of 80 as reported.

Risk of bias within studies

Details of the risk-of-bias assessment are provided in *Table 2*.

All but three trials were assessed as being at a low risk of bias for all aspects assessed. Three trials were assessed as being at an unclear risk of bias owing to high rates of loss to follow-up. In the trial by Dubnov-Raz *et al.*,[64] 52% of participants did not complete all symptom questionnaires. In the trial by Laaksi *et al.*,[55] 37% of randomised participants were lost to follow-up. In the trial by Kerley *et al.*,[67] 24% of randomised participants were lost to follow-up.

Overall results: acute respiratory infection incidence

The results of the one-step IPD meta-analysis testing the effects of vitamin D on the proportion of all participants experiencing at least one ARI, adjusting for age, sex and study duration, are presented in *Table 3*. Vitamin D supplementation resulted in a statistically significant reduction in the proportion of participants experiencing at least one ARI [adjusted odds ratio (aOR) 0.88, 95% CI 0.81 to 0.96, $p = 0.003$; p for heterogeneity < 0.001; NNT 33, 95% CI 20 to 101; 10,933 participants in 25 studies; Cates plot, *Figure 4*].

Statistically significant protective effects of vitamin D were also seen for the one-step analyses of ARI rate [adjusted incidence rate ratio (aIRR) 0.96, 95% CI 0.92 to 0.997; $p = 0.04$ and p for heterogeneity < 0.001] in 10,703 participants in 25 studies (*Table 4*). However, the protective effects of vitamin D were not seen in the analysis of time to first ARI [adjusted hazard ratio (aHR) 0.95, 95% CI 0.89 to 1.01; $p = 0.09$ and p for heterogeneity < 0.001] in 9108 participants in 18 studies (*Table 5*). Two-step analyses also showed consistent effects for the proportion of participants experiencing at least one ARI (aOR 0.80, 95% CI 0.69 to 0.93; $p = 0.004$ and p for heterogeneity $= 0.001$) in 10,899 participants in 24 studies (*Figure 5*), ARI rate (aIRR 0.91, 95% CI 0.84 to 0.98; $p = 0.018$ and p for heterogeneity < 0.001) in 10,703 participants in 25 studies, and time to first ARI (aHR 0.92, 95% CI 0.85 to 1.00; $p = 0.051$ and p for heterogeneity $= 0.14$) in 9108 participants in 18 studies. This evidence was assessed as being of high quality.

TABLE 1 Characteristics of the trials contributing data to analyses, and their participants

First author and year	Setting	Participants	Mean age (years) (SD) [range]	Male : female	25(OH)D assay, EQA scheme	Mean baseline 25(OH)D concentration (nmol/l) (SD) [range]	Baseline 25(OH)D concentration < 25 nmol/l (%)	Intervention : control	Oral dose of vitamin D_3, intervention arm	Control	Study duration	Outcome	ARI definition	*n* entering analysis/*N* randomised (%)
Li-Ng 2009[53]	USA	Healthy adults	57.9 (13.6) [21.4–80.6]	34 : 128	RIA (DiaSorin, Saluggia, Italy)	63.7 (25.5) [16.0–156.0]	3/150 (2.0)	84 : 78	50 µg daily	Placebo	3 months	ARI (1y)	URI: ≥ 2 URI symptoms in absence of allergy symptoms	157/162 (96.9)
Urashima 2010[45]	Japan	Schoolchildren	10.2 (2.3) [6.0–15.0)	242 : 188	–	Not determined	–	217 : 213	30 µg daily	Placebo	4 months	ARI (1y), asthma exacerbation. (2y in subset)	URI: influenza A/B diagnosed by RIDT or RIDT-negative ILI	334/430 (77.7), ARI; 99/110, asthma exacerbation
Manaseki-Holland 2010[54]	Afghanistan	Pre-school children with pneumonia	1.1 (0.8) [0.1–3.3]	257 : 196	–	Not determined	–	224 : 229	2.5-mg bolus, once	Placebo	3 months	ARI (2y)	LRI: repeat episode of pneumonia – age-specific tachypnoea without wheeze	453/453 (100.0)
Laaksi 2010[55]	Finland	Military conscripts	19.1 (0.6) [18.0–21.0]	164 : 0	EIA [Immunodiagnostic Systems Holdings plc (IDS), The Boldons, UK; Octeia®]	75.9 (18.7) [41.9–129.0]	0/73 (0.0)	80 : 84	10 µg daily	Placebo	6 months	ARI (1y)	ARI: medical record diagnosis	164/164 (100.0)
Majak 2011[56]	Poland	Children with asthma	10.9 (3.3) [6.0–17.0]	32 : 16	RIA (BioSource Europe, S.A., Nivelles, Belgium)	88.9 (38.2) [31.5–184.7]	0/48 (0.0)	24 : 24	12.5 µg daily	Placebo	6 months	Asthma exacerbation (1y), ARI (2y)	ARI: self-report	48/48 (100.0), asthma exacerbation and ARI
Trilok Kumar 2011[57]	India	Low-birthweight infants	0.1 (0.0) [0.0–0.3]	970 : 1109	–	Not determined	Not determined	1039 : 1040	35 µg weekly	Placebo	6 months	ARI (2y)	ARI: medical record diagnosis of events causing hospitalisation	2064/2079 (99.3)
Lehouck 2012[28]	Belgium	Adults with COPD	67.9 (8.3) [48.0–86.0]	145 : 37	RIA (DiaSorin)	49.8 (29.2) [9.0–159.7]	31/182 (17.0)	91 : 91	2.5-mg bolus monthly	Placebo	1 year	COPD exacerbation (1y), ARI (2y)	URI: self-report	175/182 (96.2), ARI; 180/182 COPD exacerbation
Manaseki-Holland 2012[58]	Afghanistan	Infants	0.5 (0.3) [0.0–1.0]	1591 : 1455	–	Not determined	Not determined	1524 : 1522	2.5-mg bolus once every 3 months	Placebo	1.5 years	ARI (1y)	LRI: pneumonia confirmed by chest radiograph	3011/3046 (98.9)
Camargo 2012[39]	Mongolia	Third/fourth grade schoolchildren	10.0 (0.9) [7.0–12.7]	129 : 118	LC-MS/MS	18.9 (9.7) [3.3–61.2]	192/245 (78.4)	143 : 104	7.5 µg daily	Placebo	7 weeks	ARI (2y)	ARI: parent-reported 'chest infections or colds'	244/247 (98.8)

First author and year	Setting	Participants	Mean age (years) (SD) [range]	Male : female	25(OH)D assay, EQA scheme	Mean baseline 25(OH)D concentration (nmol/l) (SD) [range]	Baseline 25(OH)D concentration < 25 nmol/l (%)	Intervention : control	Oral dose of vitamin D_3, intervention arm	Control	Study duration	Outcome	ARI definition	*n* entering analysis/*N* randomised (%)
Murdoch 2012[40]	New Zealand	Healthy adults	48.1 (9.7) [18.0–67.6]	81 : 241	LC-MS/MS	72.1 (22.1) [13.0–142.0]	5/322 (1.6)	161 : 161	2 × 5-mg bolus monthly, then 2.5-mg bolus monthly	Placebo	1.5 years	ARI (1y)	URI: assessed with symptom score	322/322 (100.0)
Bergman 2012[59]	Sweden	Adults with increased susceptibility to ARI	53.1 (13.1) [20.0–77.0]	38 : 102	CLA (DiaSorin)	49.3 (23.2) [8.0–135.0]	15/131 (11.45)	70 : 70	100 µg daily	Placebo	1 year	ARI (2y)	URI: assessed with symptom score	124/140 (88.6)
Marchisio 2013[60]	Italy	Children with recurrent acute otitis media	2.8 (1.0) [1.3–4.8]	64 : 52	CLA (DiaSorin)	65.3 (17.3) [24.7–120.6]	2/116 (1.7)	58 : 58	25 µg daily	Placebo	6 months	ARI (1y)	URI: doctor-diagnosed acute otitis media	116/116 (100.0)
Rees 2013[41]	USA	Adults with previous colorectal adenoma	61.2 (6.6) [47.1–77.9]	438 : 321[a]	RIA (IDS)	62.5 (21.3) [30.2–171.6]	0/759 (0.0)	399 : 360	25 µg daily	Placebo	13 months (average)	ARI (2y)	URI: assessed from daily symptom diary	759/759 (100.0)
Tran 2014[43]	Australia	Healthy older adults	71.7 (6.9) [60.3–85.2]	343 : 301	CLA (DiaSorin)	41.7 (13.5) [12.6–105.0]	66/643 (10.3)	430 : 214	0.75-mg bolus vs. 1.5-mg bolus monthly	Placebo	1 year	ARI (2y)	URI: self-reported cold	594/644 (92.2)
Goodall 2014[61]	Canada	Healthy university students	19.6 (2.2) [17.0–33.0]	218 : 382	–	Not determined	–	300 : 300	0.25 mg weekly (factorial with gargling)	Placebo	8 weeks	ARI (1y)	URI: self-reported cold	492/600 (82.0)
Urashima 2014[44]	Japan	High school students	16.5 (1.0) [15.0–18.0]	162 : 85	–	Not determined	–	148 : 99	50 µg daily	Placebo	2 months	ARI (1y)	URI: influenza A diagnosed by RIDT or RIDT-negative ILI	247/247 (100.0)
Grant 2015[62]	New Zealand	Pregnant women and offspring	unborn	0 : 260 (mothers) 121 : 128 (offspring)	LC-MS/MS	54.8 (25.8) [8.0–128.0]	30/200 (15.0)	173 : 87 (mothers) 164 : 85 (offspring)	Mothers: 25 µg vs. 50 µg daily; infants: 10 µg vs. 20 µg daily	Placebo	9 months (3 months in pregnancy and 6 months in infancy)	ARI (2y)	ARI: doctor-diagnosed ARI precipitating primary care consultation	236/260 (90.8)
Martineau 2015[29] (ViDiCO)	UK	Adults with COPD	64.7 (8.5) [40.0–85.0]	144 : 96	LC-MS/MS	46.1 (25.7) [0.0–160.0]	50/240 (20.8)	122 : 118	3-mg bolus once every 2 months	Placebo	1 year	ARI and COPD exacerbation (Co1y)	URI: assessed from daily symptom diary	240/240 (100.0), ARI and COPD exacerbation
Martineau 2015[47] (ViDiAs)	UK	Adults with asthma	47.9 (14.4) [16.0–78.0]	109 : 141	LC-MS/MS	49.6 (24.7) [0.0–139.0]	36/250 (14.4)	125 : 125	3-mg bolus once every 2 months	Placebo	1 year	ARI and asthma exacerbation (Co1y)	URI: assessed from daily symptom diary	250/250 (100.0), ARI and asthma exacerbation

continued

TABLE 1 Characteristics of the trials contributing data to analyses, and their participants (*continued*)

First author and year	Setting	Participants	Mean age (years) (SD) [range]	Male : female	25(OH)D assay, EQA scheme	Mean baseline 25(OH)D concentration (nmol/l) (SD) [range]	Baseline 25(OH)D concentration < 25 nmol/l (%)	Intervention : control	Oral dose of vitamin D_3, intervention arm	Control	Study duration	Outcome	ARI definition	*n* entering analysis/*N* randomised (%)
Martineau 2015[48] (ViDiFlu)	UK	Older adults and their carers	67.1 (13.0) [21.4–94.0]	82 : 158	LC-MS/MS	42.9 (23.0) [0.0–128.0]	60/240 (25.0)	137 : 103	Older adults: 2.4-mg bolus once every 2 months + 10 µg daily Carers: 3 mg once every 2 months	Older adults: placebo + 10 µg daily Carers: placebo	1 year	ARI (1y)	URI and LRI, both assessed from daily symptom diary	240/240 (100.0)
Simpson 2015[63]	Australia	Healthy adults	32.2 (12.2) [18.0–52.0]	14 : 20	LC-MS/MS	67.9 (23.0) [32.0–132.0]	0/33 (0.0)	18 : 16	0.5 mg weekly	Placebo	17 weeks	ARI (1y)	ARI assessed with symptom score	34/34 (100.0)
Dubnov-Raz 2015[64]	Israel	Adolescent swimmers with vitamin D insufficiency	15.2 (1.6) [12.9–18.6]	34 : 20	RIA (DiaSorin)	60.4 (11.9) [28.0–74.6]	0/54 (0.0)	27 : 27	50 µg daily	Placebo	12 weeks	ARI (1y)	URI assessed with symptom score	25/54 (46.3)
Castro 2014[65]/ Denlinger 2016[66]	USA	Adults with asthma	39.2 (12.9) [18.0–85.0]	130 : 278	CLA (DiaSorin)	47.0 (16.9) [10.0–74.6]	55/408 (13.5)	201 : 207	2.5-mg bolus then 100 µg daily	Placebo	28 weeks	Asthma exacerbation (2y), ARI (2y)	URI assessed with symptom score	408/408 (100.0), ARI and asthma exacerbation
Tachimoto 2016[42]	Japan	Children with asthma	9.9 (2.3) [6.0–15.0]	50 : 39	RIA (DiaSorin)	74.9 (24.6) [20.0–187.2]	1/89 (1.1)	54 : 35	20 µg daily, first 2 months	Placebo	6 months	Asthma exacerbation (2y), ARI (2y)	URI: assessed with symptom score	89/89 (100.0), ARI and asthma exacerbation
Kerley 2016[67]	Ireland	School children with asthma	8.6 (2.8) [5.0–15.0]	24 : 15	LC-MS/MS	54.4 (17.4) [26–92]	0/39 (0.0)	17 : 22	50 µg daily	Placebo	15 weeks	Asthma exacerbation (2y)	n/a	39/51 (76.5)
Jensen 2016[68]	Canada	Preschool children with asthma	2.9 (1.1) [1.6–5.5)	7 : 15	LC-MS/MS	64.2 (14.0)	0/22 (0.0)	11 : 11	2.5-mg bolus then 10 µg daily	10 µg daily	6 months	Asthma exacerbation (2y)	n/a	22/22 (100.0)
Ginde 2017[69]	USA	Institutionalised older adults	80.7 (9.9) [60.0–95.0]	45 : 62	LC-MS/MS	57.3 (22.7) [11.7–106.1]	12/107 (11.2)	55 : 52	2.5-mg bolus monthly + ≤ 25 µg per day equivalent	Placebo + 10–25 µg per day equivalent	1 year	ARI (1y)	ARI: medical record diagnosis	107/107 (100.0)

1y, primary outcome; 2y, secondary outcome; CLA, chemiluminescent assay; EIA, enzyme immunoassay; EQA, external quality assessment; ILI, influenza-like illness; LC-MS/MS, liquid chromatography tandem-mass spectrometry; n/a, not applicable; RIA, radioimmunoassay; RIDT, rapid influenza diagnostic test.

a Sex missing for two participants randomised to intervention arm and subsequently excluded from analysis as a result of a lack of outcome data.

Notes

1 µg vitamin $D_3 = 40$ IU.

25(OH)D concentrations reported in ng/ml were converted to nmol/l by multiplying by 2.496.

TABLE 2 Risk-of-bias assessment

First author and year	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Li-Ng 2009[53]	✓	✓	✓	✓	✓	✓	✓
Urashima 2010[45]	✓	✓	✓	✓	✓	✓	✓
Manaseki-Holland 2010[54]	✓	✓	✓	✓	✓	✓	✓
Laaksi 2010[55]	✓	✓	✓	✓	?	✓	✓
Majak 2011[56]	✓	✓	✓	✓	✓	✓	✓
Trilok Kumar 2011[57]	✓	✓	✓	✓	✓	✓	✓
Lehouck 2012[28]	✓	✓	✓	✓	✓	✓	✓
Manaseki-Holland 2012[58]	✓	✓	✓	✓	✓	✓	✓
Camargo 2012[39]	✓	✓	✓	✓	✓	✓	✓
Murdoch 2012[40]	✓	✓	✓	✓	✓	✓	✓
Bergman 2012[59]	✓	✓	✓	✓	✓	✓	✓
Marchisio 2013[60]	✓	✓	✓	✓	✓	✓	✓
Rees 2013[41]	✓	✓	✓	✓	✓	✓	✓
Tran 2014[43]	✓	✓	✓	✓	✓	✓	✓
Goodall 2014[61]	✓	✓	✓	✓	✓	✓	✓
Urashima 2014[44]	✓	✓	✓	✓	✓	✓	✓
Grant 2015[62]	✓	✓	✓	✓	✓	✓	✓
Martineau 2015[29] (ViDiCO)	✓	✓	✓	✓	✓	✓	✓
Martineau 2015[47] (ViDiAs)	✓	✓	✓	✓	✓	✓	✓
Martineau 2015[48] (ViDiFlu)	✓	✓	✓	✓	✓	✓	✓
Simpson 2015[63]	✓	✓	✓	✓	✓	✓	✓
Dubnov-Raz 2015[64]	✓	✓	✓	✓	?	✓	✓
Denlinger 2016[66]	✓	✓	✓	✓	✓	✓	✓
Tachimoto 2016[42]	✓	✓	✓	✓	✓	✓	✓
Kerley 2016[67]	✓	✓	✓	✓	?	✓	✓
Jensen 2016[68]	✓	✓	✓	✓	✓	✓	✓
Ginde 2017[69]	✓	✓	✓	✓	✓	✓	✓

✓, low risk of bias; ?, unclear risk of bias.

TABLE 3 One-step IPD meta-analysis, proportion of participants experiencing at least one ARI: overall and by subgroup

Subgroup	Number of trials[a]	Proportion with ≥ 1 ARI subgroup (%)		aOR (95% CI)[b]	*p*-value	*p*-value for interaction
		Control	Intervention			
Overall	25	2204/5225 (42.2)	2303/5708 (40.3)	0.88 (0.81 to 0.96)	0.003	–
Baseline 25(OH)D (nmol/l)						
< 25	14	137/249 (55.0)	117/289 (40.5)	0.58 (0.40 to 0.82)	0.002	0.01
≥ 25	19	1027/1639 (62.7)	1179/1995 (59.1)	0.89 (0.77 to 1.04)	0.15	
Dosing regimen type						
Bolus dose ≥ 30,000 IU given	10	994/2786 (35.7)	1097/3014 (36.4)	0.97 (0.86 to 1.10)	0.67	0.05
Bolus dose not given	15	1210/2439 (49.6)	1206/2694 (44.8)	0.81 (0.72 to 0.91)	< 0.001	
Daily dose equivalent (IU)						
< 800	5	629/1321 (47.6)	619/1435 (43.1)	0.80 (0.68 to 0.94)	0.006	0.12
800–1999.9	9	945/2796 (33.8)	1023/3077 (33.2)	0.90 (0.79 to 1.01)	0.08	
≥ 2000	11	630/1108 (56.9)	661/1196 (55.3)	0.98 (0.81 to 1.18)	0.84	
Age (years)						
≤ 1	4	832/2744 (30.3)	854/2827 (30.2)	0.94 (0.83 to 1.06)	0.33	0.61
1.1–15.9	8	241/513 (47.0)	194/566 (34.3)	0.60 (0.46 to 0.77)	< 0.001	
16–65	17	854/1459 (58.5)	885/1592 (55.6)	0.93 (0.79 to 1.10)	0.41	
> 65	11	277/509 (54.4)	370/723 (51.2)	0.86 (0.67 to 1.09)	0.21	
Body mass index (kg/m^2)						
< 25	19	972/1943 (50.0)	956/2074 (46.1)	0.85 (0.74 to 0.97)	0.02	0.29
≥ 25	17	659/1039 (63.4)	754/1235 (61.1)	0.95 (0.79 to 1.14)	0.58	
Comorbidity: asthma						
No	11	518/1008 (51.4)	520/1101 (47.2)	0.82 (0.68 to 0.99)	0.04	0.48
Yes	11	296/534 (55.4)	285/542 (52.6)	0.95 (0.73 to 1.25)	0.73	
Comorbidity: COPD						
No	7	477/763 (62.5)	493/791 (62.3)	1.00 (0.80 to 1.26)	0.98	0.38
Yes	6	122/230 (53.0)	120/238 (50.4)	0.84 (0.57 to 1.24)	0.38	
Influenza vaccination						
No	10	255/373 (68.4)	253/407 (62.2)	0.74 (0.52 to 1.03)	0.08	0.51
Yes	10	564/779 (72.4)	577/826 (69.9)	0.86 (0.68 to 1.09)	0.22	

aOR, adjusted odds ratio.

a Some trials did not contribute data to a given subgroup, either because individuals within that subgroup were not represented, or because data relating to the potential effect modifier were not recorded; accordingly the number of trials represented varies between subgroups.

b Adjusted for age, sex and study duration.

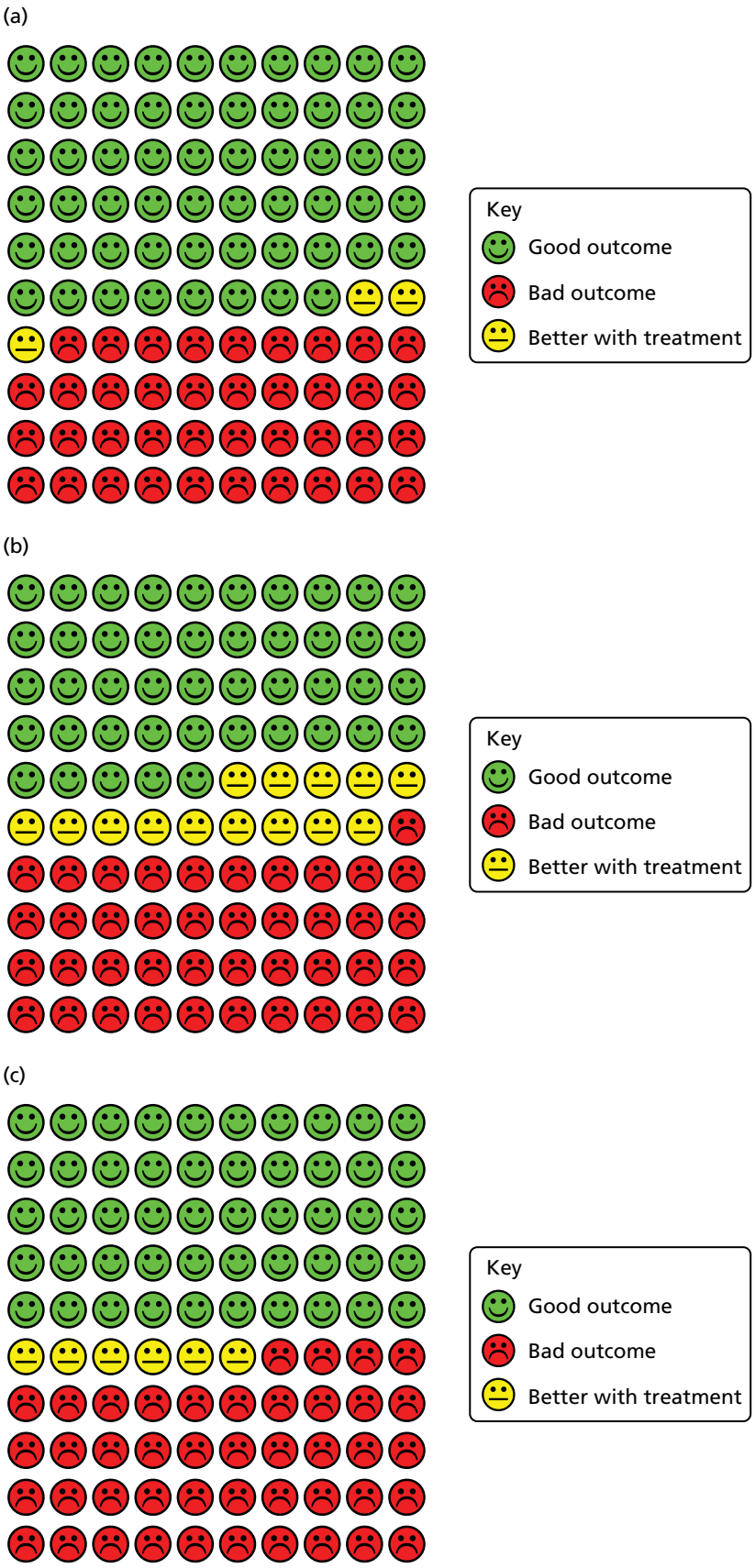

FIGURE 4 Cates plots illustrating reduction in risk of ARI with vitamin D supplementation, irrespective of dosing frequency. (a) All participants, irrespective of baseline vitamin D status; (b) participants with baseline serum 25(OH)D concentration of < 25 nmol/l; and (c) participants receiving daily or weekly vitamin D supplementation regimens without any additional bolus doses.

TABLE 4 One-step IPD meta-analysis, ARI event rate: overall effect and subgroup analyses by baseline vitamin D status and dosing regimen

Subgroup	Number of trials	Number of individuals	Rate of ARI per participant-year, subgroup		aIRR (95% CI)[a]	*p*-value	*p*-value for Interaction
			Control	Intervention			
Overall	25	10,703	1.15	1.13	0.96 (0.92 to 0.997)	0.04	–
Baseline 25(OH)D (nmol/l)							
< 25	14	509	2.15	1.67	0.78 (0.66 to 0.93)	0.004	0.02
≥ 25	19	3458	2.12	1.91	0.95 (0.90 to 1.00)	0.04	
Dosing regimen type							
Bolus dose ≥ 30,000 IU given	10	5595	0.73	0.76	0.99 (0.94 to 1.05)	0.83	0.11
Bolus dose not given	15	5133	2.23	2.09	0.93 (0.88 to 0.98)	0.008	

a Adjusted for age, sex and study duration.

TABLE 5 One-step IPD meta-analysis, time to first ARI: overall effect and subgroup analyses by baseline vitamin D status and dosing regimen

Subgroup	Number of trials	Number of individuals	Median time (days) to first ARI, subgroup (IQR)		aHR (95% CI)[a]	*p*-value	*p*-value for Interaction
			Control	Intervention			
Overall	18	9108	452 (79 to –)	502 (81 to –)	0.95 (0.89 to 1.01)	0.09	–
Baseline 25(OH)D (nmol/l)							
< 25	10	229	159 (56 to –)	172 (74 to –)	0.92 (0.66 to 1.28)	0.62	0.61
≥ 25	12	2231	104 (41 to 280)	110 (40 to 328)	0.97 (0.88 to 1.06)	0.48	
Dosing regimen type							
Bolus dose ≥ 30,000 IU given	8	4795	– (121 to –)	– (117 to –)	0.98 (0.89 to 1.08)	0.74	0.30
Bolus dose not given	10	4313	138 (57 to 331)	153 (61 to 351)	0.91 (0.84 to 0.99)	0.04	

–, these values cannot be defined.
a Adjusted for age, sex and study duration.

Overall results: asthma exacerbation

One-step IPD meta-analysis testing the effects of vitamin D on the rate of asthma exacerbations requiring treatment with systemic corticosteroids revealed a statistically significant protective effect of the intervention (aIRR 0.74, 95% CI 0.56 to 0.97; $p = 0.03$; 955 participants in seven studies). Two-step IPD meta-analysis revealed a similar effect size (aIRR 0.69, 95% CI 0.52 to 0.92, $p = 0.01$; p for heterogeneity = 0.56; 719 participants in four studies). Consistent trends were seen for analysis of the proportion of participants experiencing at least one asthma exacerbation requiring treatment with systemic corticosteroids in both one-step analysis (aOR 0.75, 95% CI 0.51 to 1.09; $p = 0.13$; 955 participants in seven studies) and two-step analysis (aOR 0.69, 95% CI 0.46 to 1.02, $p = 0.06$; p for heterogeneity = 0.74; 719 participants in four studies).

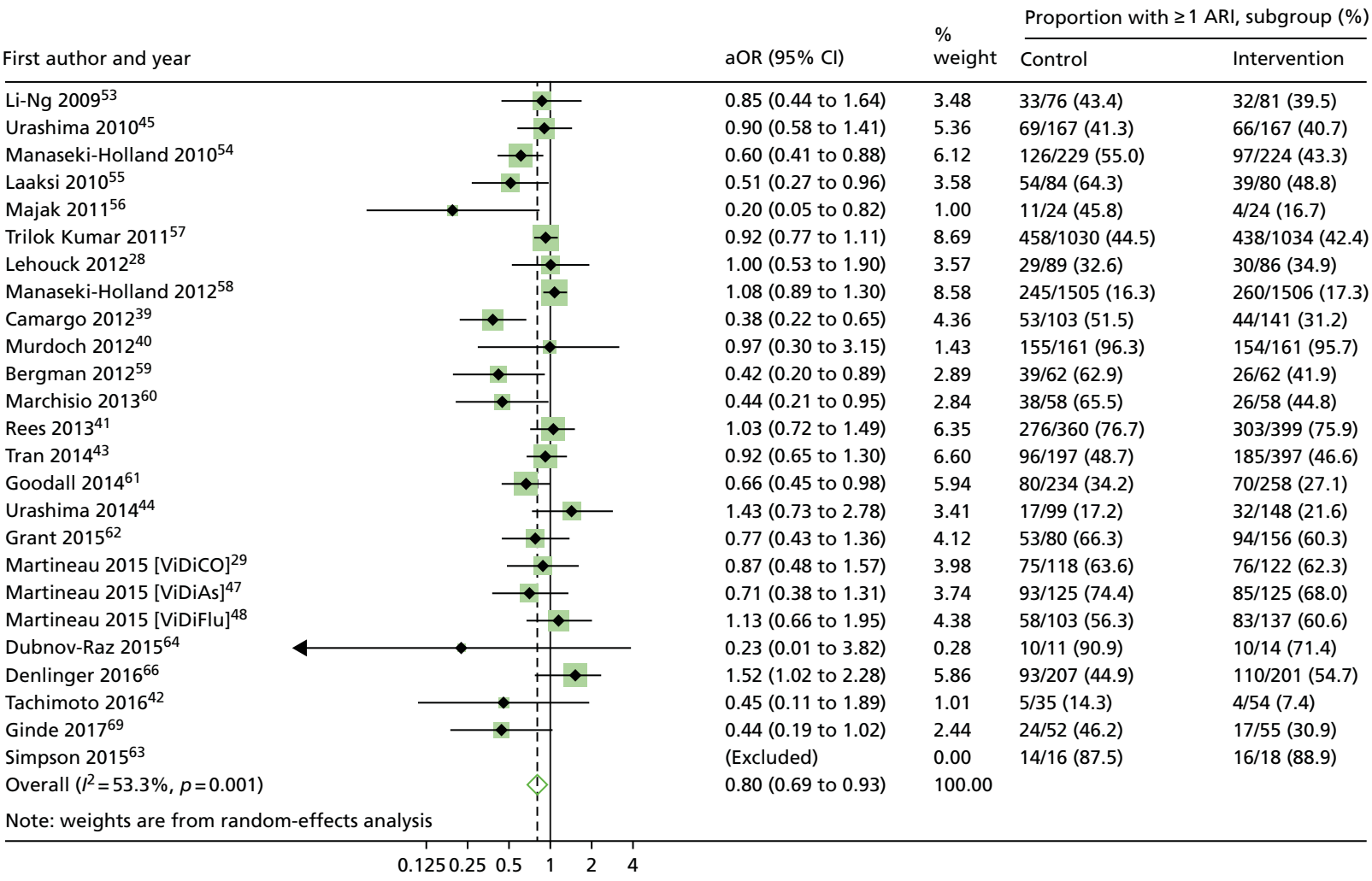

FIGURE 5 Two-step IPD meta-analysis, proportion of participants experiencing at least one ARI. Data from the trial by Simpson *et al.*[63] were not included in this two-step meta-analysis, as an estimate for the effect of the intervention in the study could not be obtained in the regression model because of the small sample size.

Similarly, trends towards a delay to first exacerbation with vitamin D versus placebo were seen in both one-step analysis (aHR 0.78, 95% CI 0.55 to 1.10; $p = 0.16$; 868 participants in five studies) and two-step analysis (aHR 0.74, 95% CI 0.52 to 1.05, $p = 0.09$; p for heterogeneity = 0.58; 680 participants in three studies).

Overall results: chronic obstructive pulmonary disease exacerbation

One-step IPD meta-analysis testing the effects of vitamin D on the rate of COPD exacerbations requiring treatment with antibiotics and/or systemic corticosteroids did not reveal a statistically significant protective effect of the intervention overall (aIRR 0.95, 95% CI 0.82 to 1.10; $p = 0.50$; 422 participants in two studies). Two-step IPD meta-analysis revealed a similar estimate (aIRR 0.96, 95% CI 0.83 to 1.10; $p = 0.54$; 422 participants in two studies). Consistent results were seen for analysis of the proportion of participants experiencing at least one study-defined exacerbation in both one-step IPD meta-analysis (aOR 0.80, 95% CI 0.51 to 1.25; $p = 0.32$; 422 participants in two studies) and two-step IPD meta-analysis (aOR 0.79, 95% CI 0.50 to 1.24; $p = 0.31$; 422 participants in two studies). Similarly, no statistically significant effects of the intervention on time to first exacerbation were seen for one-step IPD meta-analysis (aHR 0.95, 95% CI 0.75 to 1.21; $p = 0.67$; 422 participants in two studies) or two-step IPD meta-analysis (aHR 0.96, 95% CI 0.76 to 1.22; $p = 0.75$; 422 participants in two studies) overall.

Subgroup analyses: acute respiratory infection incidence

In order to explore reasons for heterogeneity, subgroup analyses were conducted to investigate whether or not the effects of vitamin D supplementation on ARI risk differed according to baseline vitamin D status, dosing frequency, dose size, age, body mass index, the presence or absence of comorbidity (asthma or COPD) or influenza vaccination status. Race/ethnicity was not investigated as a potential effect-modifier, as data for this variable were missing for 3680 out of 10,933 (34%) participants, and power for subgroup analyses was limited by small numbers in many racial/ethnic subgroups that could not be meaningfully combined. Similarly, baseline data relating to environmental exposure to particulate matter, nutritional supplement use and vitamin D-related genotype were unavailable or available only in a very small number of studies, precluding investigation of these factors as potential effect modifiers. The results are presented in *Overall results: acute respiratory infection incidence* (see *Table 3*). Subgroup analysis revealed a strong protective effect of vitamin D supplementation among individuals at a baseline circulating 25(OH)D concentration level of < 25 nmol/l (aOR 0.58, 95% CI 0.40 to 0.82; NNT 8, 95% CI 5 to 21; 538 participants in 14 studies; within subgroup, $p = 0.002$; Cates plot, see *Figure 4*), and no statistically significant effect among those at a baseline 25(OH)D concentration level of ≥ 25 nmol/l (aOR 0.89, 95% CI 0.77 to 1.04; 3634 participants in 19 studies; within subgroup, $p = 0.15$; for interaction, $p = 0.01$). This evidence was assessed as being of high quality.

A meta-analysis of data from trials in which vitamin D was administered using a daily or weekly regimen without additional bolus doses revealed a protective effect of vitamin D against ARI (aOR 0.81, 95% CI 0.72 to 0.91; NNT 20, 95% CI 13 to 43; 5133 participants in 15 studies; within subgroup, $p < 0.001$; Cates plot, see *Figure 4*). No such protective effect was seen among participants in trials in which at least one bolus dose of vitamin D was administered (aOR 0.97, 95% CI 0.86 to 1.10; 5800 participants in 10 studies; within subgroup, $p = 0.67$; for interaction, $p = 0.05$). This evidence was assessed as being of high quality. The p-values for interaction were > 0.05 for all other potential effect modifiers investigated. For both of these subgroup analyses, broadly consistent effects were observed for event rate analysis (see *Table 4*) and survival analysis (see *Table 5*).

Having identified two potential factors that modified the influence of vitamin D supplementation on the risk of ARI (i.e. baseline vitamin D status and dosing frequency), we then proceeded to investigate whether or not these factors were acting as independent effect modifiers, and whether or not they were confounded by each other or by another potential effect modifier, such as age. Dot plots revealed a trend towards lower median baseline serum 25(OH)D concentration and higher median age for studies employing bolus versus daily or weekly dosing (*Figures 6* and *7*). In order to establish which of these potential effect modifiers was acting independently, we repeated the analysis to include treatment–covariate interaction terms for baseline vitamin D status, dosing frequency and age. In this model, interaction terms for baseline vitamin D

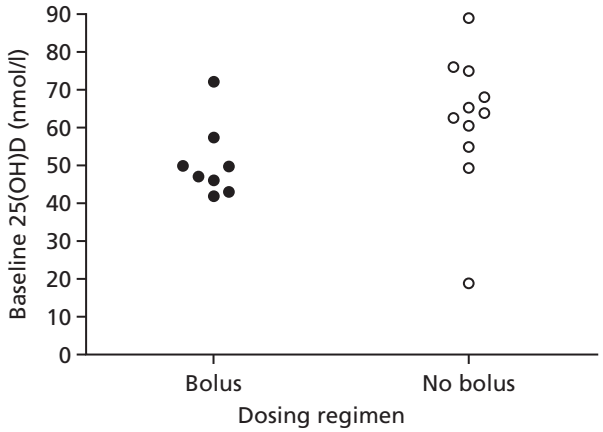

FIGURE 6 Mean baseline serum 25(OH)D concentration at enrolment by dosing regimen. Bolus, studies in which a bolus dose of ≥ 30,000 IU of vitamin D was given in the intervention arm; No bolus, studies in which vitamin D was administered daily or weekly without administration of a bolus dose.

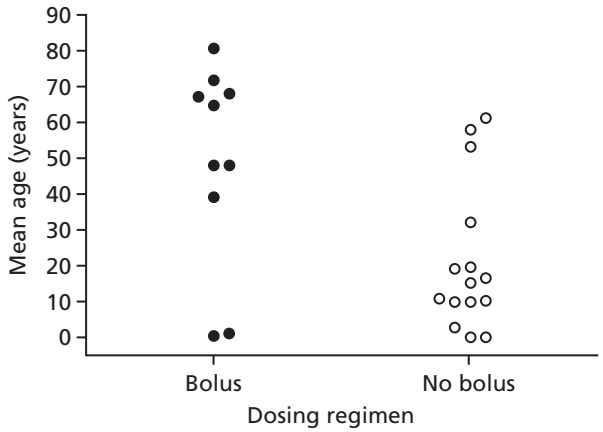

FIGURE 7 Mean age at enrolment by dosing regimen. Bolus, studies in which a bolus dose of ≥ 30,000 IU of vitamin D was given in the intervention arm; No bolus, studies in which vitamin D was administered daily or weekly without administration of a bolus dose.

status and dosing frequency were statistically significant ($p = 0.01$ and $p = 0.004$, respectively), but the interaction term for age was not statistically significant ($p = 0.20$), consistent with the hypothesis that baseline vitamin D status and dosing frequency, but not age, independently modified the effect of vitamin D supplementation on ARI risk.

We then proceeded to stratify the subgroup analysis presented in *Table 3* according to dosing frequency, in order to provide a 'cleaner' look at the results of the subgroup analyses under the assumption that administration of bolus doses was ineffective. The results of this exploratory analysis are presented in *Table 6*.

This analysis reveals that daily or weekly administration of vitamin D was associated with an even greater degree of protection against ARI among participants with baseline circulating 25(OH)D concentrations of < 25 nmol/l than in the unstratified analysis (aOR 0.30, 95% CI 0.17 to 0.53; NNT 4, 95% CI 3 to 7; 234 participants in six studies; within subgroup, $p < 0.001$; Cates plot, *Figure 8*). Moreover, administration of daily or weekly vitamin D also protected against ARI among participants with higher baseline 25(OH)D concentrations (aOR 0.75, 95% CI 0.60 to 0.95; NNT 15, 95% CI 9 to 86; 1603 participants in six studies; within subgroup, $p = 0.02$; Cates plot, see *Figure 8*). The *p*-value for interaction for this subgroup analysis was 0.006, indicating that protective effects of daily or weekly vitamin D supplementation were significantly greater in the subgroup of participants with profound vitamin D deficiency. No other statistically significant interaction was seen; notably, bolus-dose vitamin D supplementation did not offer any protection against ARI even when administered to those with circulating 25(OH)D concentrations of < 25 nmol/l (aOR 0.82, 95% CI 0.51 to 1.33; 304 participants in eight studies; within subgroup, $p = 0.43$).

TABLE 6 One-step IPD meta-analysis, proportion of participants experiencing at least one ARI: overall and by subgroup, stratified by dosing frequency

	Bolus						Daily or weekly					
		Proportion with ≥ 1 ARI subgroup (%)						Proportion with ≥ 1 ARI subgroup (%)				
Subgroup	Number of trials[a]	Control	Intervention	aOR (95% CI)[b]	*p*-value	*p*-value for interaction	Number of trials[a]	Control	Intervention	aOR (95% CI)[b]	*p*-value	*p*-value for interaction
Overall	10	994/2786 (35.7)	1097/3014 (36.4)	0.97 (0.86 to 1.10)	0.67	N/A	15	1210/2439 (49.6)	1206/2694 (44.8)	0.81 (0.72 to 0.91)	0.001	N/A
Baseline 25(OH)D (nmol/l)												
< 25	8	73/142 (51.4)	77/162 (47.5)	0.82 (0.51 to 1.33)	0.43	0.42	6	64/107 (59.8)	40/127 (31.5)	0.30 (0.17 to 0.53)	< 0.001	0.006
≥ 25	8	550/910 (60.4)	663/1121 (59.1)	1.02 (0.83 to 1.24)	0.87		11	477/729 (65.4)	516/874 (59.0)	0.75 (0.60 to 0.95)	0.02	
Daily dose equivalent (IU)												
< 800	0	N/A	N/A	N/A	N/A	0.56	5	629/1321 (47.6)	619/1435 (43.1)	0.80 (0.68 to 0.94)	0.006	0.82
800–1999.9	3	467/1931 (24.2)	542/2127 (25.5)	0.95 (0.81 to 1.10)	0.50		6	478/865 (55.3)	481/950 (50.6)	0.81 (0.66 to 1.01)	0.06	
≥ 2000	7	527/855 (61.6)	555/887 (62.6)	1.03 (0.83 to 1.28)	0.81		4	103/253 (40.7)	106/309 (34.3)	0.85 (0.58 to 1.24)	0.39	
Age (years)												
≤ 1	2	321/1634 (19.6)	322/1637 (19.7)	0.99 (0.83 to 1.19)	0.93	0.72	2	511/1110 (46.0)	532/1190 (44.7)	0.91 (0.77 to 1.08)	0.30	0.37
1.1–15.9	1	50/100 (50.0)	35/93 (37.6)	0.62 (0.35 to 1.11)	0.11		7	191/413 (46.2)	159/473 (33.6)	0.59 (0.45 to 0.79)	< 0.001	
16–65	8	432/678 (63.7)	466/716 (65.1)	1.15 (0.90 to 1.48)	0.27		9	422/781 (54.0)	419/876 (47.8)	0.79 (0.63 to 0.99)	0.04	
> 65	8	191/374 (51.1)	274/568 (48.2)	0.85 (0.65 to 1.12)	0.25		3	86/135 (63.7)	96/155 (61.9)	0.88 (0.52 to 1.52)	0.66	
Body mass index (kg/m^2)												
< 25	8	215/372 (57.8)	231/417 (55.4)	1.01 (0.72 to 1.40)	0.97	0.70	11	757/1571 (48.2)	725/1657 (43.8)	0.82 (0.71 to 0.95)	0.009	> 0.99
≥ 25	8	406/677 (60.0)	509/867 (58.7)	1.00 (0.80 to 1.25)	0.98		9	253/358 (70.7)	245/367 (66.8)	0.83 (0.59 to 1.17)	0.30	
Asthma												
No	5	303/484 (62.6)	323/523 (61.8)	0.95 (0.71 to 1.28)	0.75	0.40	6	215/524 (41.0)	197/578 (34.1)	0.74 (0.58 to 0.95)	0.02	0.40
Yes	4	224/371 (60.4)	232/364 (63.7)	1.18 (0.85 to 1.65)	0.32		7	72/163 (44.2)	53/178 (29.8)	0.60 (0.37 to 0.98)	0.04	
COPD												
No	5	410/632 (64.9)	436/656 (66.5)	–[c]	–[c]	–[c]	2	67/131 (51.1)	57/135 (42.2)	–[c]	–[c]	–[c]
Yes	4	117/223 (52.5)	119/231 (51.5)	–[c]	–[c]	–[c]	2	5/7 (71.4)	1/7 (14.3)	–[c]	–[c]	–[c]

Subgroup	Bolus						Daily or weekly					
	Number of trials[a]	Proportion with ≥ 1 ARI subgroup (%)		aOR (95% CI)[b]	*p*-value	*p*-value for interaction	Number of trials[a]	Proportion with ≥ 1 ARI subgroup (%)		aOR (95% CI)[b]	*p*-value	*p*-value for interaction
		Control	Intervention					Control	Intervention			
Influenza vaccination												
No	5	119/163 (73.0)	121/178 (68.0)	–[c]	–[c]	–[c]	5	136/210 (64.8)	132/229 (57.6)	–[c]	–[c]	–[c]
Yes	5	286/396 (72.2)	294/421 (69.8)				5	278/383 (72.6)	283/405 (69.9)			

N/A, not applicable.

a Some trials did not contribute data to a given subgroup, either because individuals within that subgroup were not represented, or because data relating to the potential effect modifier were not recorded; accordingly, the number of trials represented varies between subgroups.

b Adjusted for age, sex and study duration.

c Values could not be estimated as models did not converge.

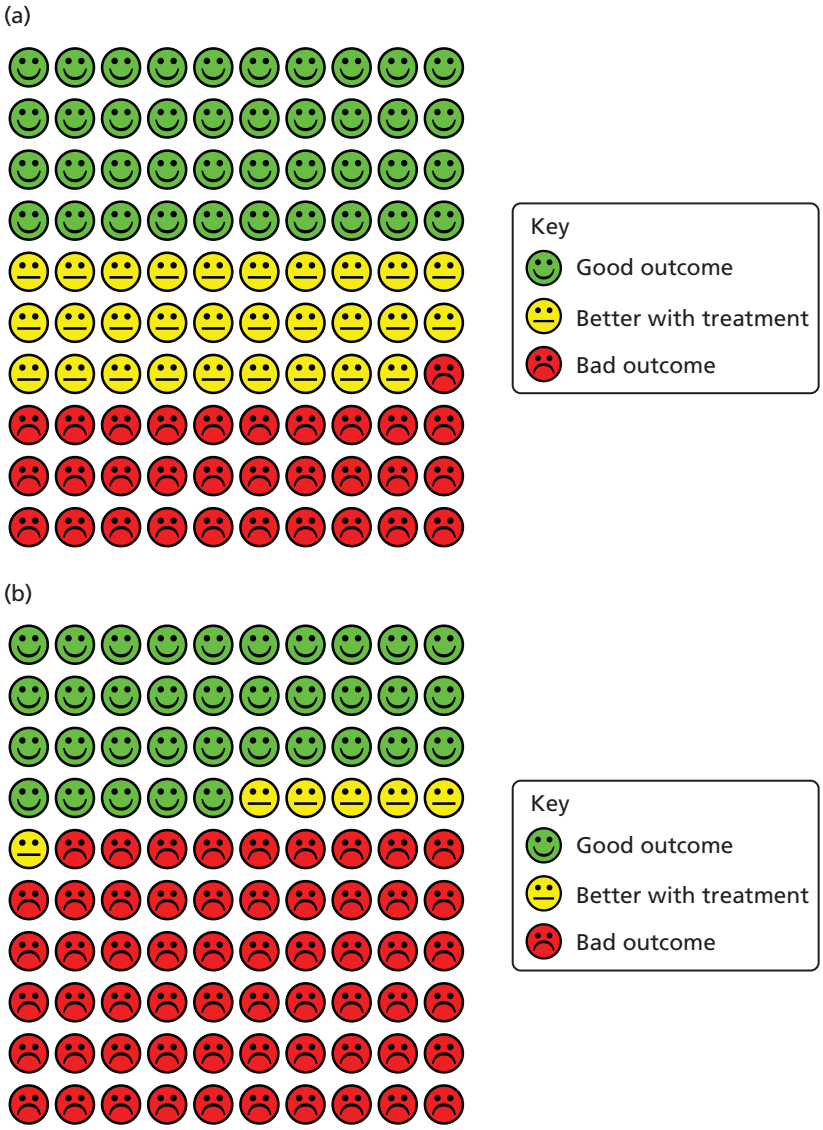

FIGURE 8 Cates plot illustrating reduction in risk of ARI with daily or weekly vitamin D supplementation without additional bolus doses. (a) Participants with baseline serum 25(OH)D concentrations of < 25 nmol/l; and (b) participants with baseline serum 25(OH)D concentrations of ≥ 25 nmol/l.

Subgroup analyses: asthma exacerbation

Subgroup analyses were conducted to investigate whether or not the effects of vitamin D supplementation on the rate of asthma exacerbations requiring treatment with systemic corticosteroids differed according to baseline vitamin D status, age, body mass index, administration of bolus doses of vitamin D, amount of vitamin D administered and concomitant use of inhaled corticosteroids. The results are presented in *Table 7*. Vitamin D supplementation reduced the rate of asthma exacerbations requiring treatment with systemic corticosteroids among individuals with baseline circulating 25(OH)D concentrations of < 25 nmol/l (aIRR 0.33, 95% CI 0.11 to 0.98; 92 participants in three studies; within subgroup, $p = 0.046$) and in those with baseline 25(OH)D concentrations of ≥ 25 nmol/l (aIRR 0.77, 95% CI 0.58 to 1.03; 764 participants in six studies within subgroup, $p = 0.08$). The treatment–covariate interaction term (ratio of aIRRs) for this subgroup analysis was 0.56 (95% CI 0.20 to 1.52; for interaction, $p = 0.25$). The p-values for interaction for all other subgroup analyses were also > 0.05.

TABLE 7 One-step IPD meta-analysis, rate of asthma exacerbations requiring treatment with systemic corticosteroids: overall and by subgroup

Subgroup	Number of trials[a]	Number of individuals	Event rate per participant-year subgroup		aIRR (95% CI)[b]	*p*-value	*p*-value for interaction
			Control	Intervention			
Overall	7	955	121/284.7 (0.43)	85/286.6 (0.30)	0.74 (0.56 to 0.97)	0.03	–
Baseline 25(OH)D (nmol/l)							
< 25	3	92	14/33.0 (0.42)	6/32.2 (0.19)	0.33 (0.11 to 0.98)	0.046	0.25
≥ 25	6	764	107/233.8 (0.46)	79/240.2 (0.33)	0.77 (0.58 to 1.03)	0.08	
Age (years)							
< 16	5	290	26/57.6 (0.45)	19/61.8 (0.31)	0.64 (0.34 to 1.20)	0.16	0.56
≥ 16	3	665	95/227.2 (0.42)	66/224.7 (0.29)	0.70 (0.51 to 0.97)	0.03	
Sex							
Female	7	547	80/163.6 (0.49)	47/167.7 (0.28)	0.61 (0.43 to 0.88)	0.008	0.17
Male	7	408	41/121.1 (0.34)	38/118.7 (0.32)	0.91 (0.58 to 1.42)	0.67	
Body habitus							
Not overweight	7	381	38/110.5 (0.34)	26/104.5 (0.25)	0.91 (0.55 to 1.51)	0.71	0.31
Overweight[c]	7	574	83/174.3 (0.48)	59/182.0 (0.32)	0.68 (0.49 to 0.95)	0.02	
Bolus-dose vitamin D given							
No	4	275	13/53.8 (0.24)	10/58.9 (0.17)	0.65 (0.26 to 1.63)	0.36	0.49
Yes	3	680	108/230.9 (0.47)	75/227.6 (0.33)	0.71 (0.52 to 0.95)	0.02	
Daily dose equivalent (IU)							
< 2000	4	258	13/52.1 (0.25)	10/58.6 (0.17)	0.62 (0.26 to 1.44)	0.26	0.78
≥ 2000	3	697	108/232.7 (0.46)	75/228.0 (0.33)	0.73 (0.54 to 0.98)	0.03	
Inhaled corticosteroids							
No	4	92	1/18.8 (0.05)	4/26.1 (0.15)	1.11 (0.07 to 18.40)	0.94	0.19
Yes	5	764	120/248.0 (0.48)	81/246.3 (0.33)	0.71 (0.54 to 0.95)	0.02	
Study duration (months)							
< 6	2	138	13/25.0 (0.52)	9/19.4 (0.46)	0.50 (0.18 to 1.37)	0.18	0.62
≥ 6	5	816	108/259.8 (0.42)	76/267.2 (0.28)	0.72 (0.53 to 0.96)	0.03	

a Some trials did not contribute data to a given subgroup, either because individuals within that subgroup were not represented, or because data relating to the potential effect modifier were not available; accordingly, the number of trials represented varies between subgroups.
b Adjusted for age and sex.
c Overweight defined as body mass index z-score ≥ 1.0 for participants aged < 19 years and as body mass index ≥ 25 kg/m^2 for participants aged ≥ 19 years.

Subgroup analyses: chronic obstructive pulmonary disease exacerbation

Subgroup analyses were conducted to investigate whether or not the effects of vitamin D supplementation on the rate of study-defined COPD exacerbation differed according to baseline vitamin D status, COPD severity, inhaled corticosteroid requirement at baseline and body mass index. The results are presented in *Table 8*. Vitamin D supplementation reduced the rate of COPD exacerbations among individuals with baseline circulating 25(OH)D concentrations of < 25 nmol/l (aIRR 0.56, 95% CI 0.39 to 0.81; 81 participants in two studies; within subgroup, $p = 0.002$) but not in those with baseline 25(OH)D concentrations of ≥ 25 nmol/l (aIRR 1.05, 95% CI 0.89 to 1.23; 341 participants in two studies; within subgroup, $p = 0.65$).

The treatment–covariate interaction term (ratio of aIRRs) for this subgroup analysis was 1.85 (95% CI 1.24 to 2.75; for interaction, $p = 0.003$). The *p*-values for interaction for other subgroup analyses were > 0.05.

Secondary outcomes: efficacy

Results of one-step IPD meta-analysis of secondary outcomes are presented in *Table 9*.

When all studies were analysed together, no statistically significant effect of vitamin D was seen on the proportion of participants with at least one URI, LRI, hospitalisation or emergency department attendance for ARI, use of a course of antimicrobials for ARI, work/school absence as a result of ARI, severe asthma exacerbation or severe COPD exacerbation. When this analysis was stratified by dosing frequency in an exploratory analysis, a borderline significant protective effect of daily or weekly vitamin D supplementation against URI was seen (aOR 0.88, 95% CI 0.78 to 1.00; 4483 participants in 11 studies, $p = 0.05$; *Table 10*).

TABLE 8 One-step IPD meta-analysis, COPD exacerbation rate: overall and by subgroup

Subgroup	Number of trials	Number of individuals	Event rate per participant-year, group subgroup		aIRR (95% CI)[a]	*p*-value	*p*-value for interaction
			Control	Intervention			
Overall	2	422	374/189.75 (1.97)	364/193.67 (1.88)	0.95 (0.82 to 1.10)	0.50	
Baseline 25(OH)D (nmol/l)							
< 25	2	81	76/35.87 (2.12)	46/39.45 (1.16)	0.56 (0.39 to 0.81)	0.002	0.003
≥ 25	2	341	298/153.88 (1.94)	318/154.23 (2.06)	1.05 (0.89 to 1.23)	0.56	
COPD severity							
GOLD stage 1/2	2	223	123/100.82 (1.22)	130/104.25 (1.25)	1.03 (0.81 to 1.32)	0.79	0.45
GOLD stage 3/4	2	199	251/88.93 (2.82)	234/89.42 (2.62)	0.92 (0.77 to 1.10)	0.37	
Concomitant inhaled corticosteroid at baseline							
No	2	112	55/45.31 (1.21)	55/53.53 (1.03)	0.91 (0.62 to 1.32)	0.61	0.70
Yes	2	310	319/144.44 (2.21)	309/140.14 (2.20)	0.97 (0.83 to 1.14)	0.72	
Body mass index (kg/m^2)							
< 25	2	199	200/97.92 (2.04)	172/82.07 (2.10)	0.99 (0.81 to 1.21)	0.91	0.70
≥ 25	2	223	174/91.83 (1.89)	192/111.60 (1.72)	0.92 (0.75 to 1.13)	0.42	

GOLD, Global Initiative for Chronic Obstructive Lung Disease.
a Adjusted for age, sex and COPD severity.

TABLE 9 One-step IPD meta-analysis of secondary outcomes

Outcome	Number of trials	Proportion with ≥ 1 event subgroup (%)		aOR (95% CI)[a]	*p*-value
		Control	Intervention		
URI	19	1656/3286 (50.4)	1807/3733 (48.4)	0.93 (0.83 to 1.03)	0.15
LRI	9	542/3285 (16.5)	561/3413 (16.4)	0.96 (0.83 to 1.10)	0.52
Hospitalisation or emergency department attendance as a result of ARI	11	47/3886 (1.2)	40/3986 (1.0)	0.83 (0.54 to 1.27)	0.39
Use of antimicrobials for treatment of ARI	9	397/983 (40.4)	413/1121 (36.8)	0.84 (0.69 to 1.03)	0.10
Work/school absence as a result of ARI	7	321/632 (50.8)	319/684 (46.6)	0.87 (0.69 to 1.09)	0.22
Serious adverse event of any cause	25	216/5371 (4.0)	221/5853 (3.8)	0.98 (0.80 to 1.20)	0.83
Death as a result of ARI/respiratory failure	25	7/5330 (0.1)	6/5802 (0.1)	0.70 (0.23 to 2.20)	0.55
Death as a result of any infection	25	15/5338 (0.3)	16/5812 (0.3)	0.95 (0.46 to 1.99)	0.90
Death as a result of any cause	25	48/5371 (0.9)	56/5853 (1.0)	1.39 (0.85 to 2.27)	0.18
Hypercalcaemia	14	9/1739 (0.5)	12/2111 (0.6)	–[b]	–[b]
Renal stones	14	4/1707 (0.2)	2/2134 (0.1)	–[b]	–[b]

a Adjusted for age, sex and study duration.
b Values could not be estimated as models did not converge.

Secondary outcomes: safety

Administration of vitamin D did not influence the risk of serious adverse events of any cause (aOR 0.98, 95% CI 0.80 to 1.20) or death attributable to any cause (aOR 1.39, 95% CI 0.85 to 2.27) (see *Table 9*). Instances of potential adverse reactions to vitamin D were rare. Hypercalcaemia was detected in 21 out of 3850 (0.5%) and renal stones were diagnosed in 6 out of 3841 (0.2%); both events were equally represented in the intervention and control arms (see *Table 9*). Stratification of this analysis by dosing frequency did not reveal any statistically significant increase in the risk of adverse events with either bolus or daily or weekly supplementation (see *Table 10*).

Risk of bias across studies

A funnel plot for the proportion of participants experiencing at least one ARI showed a degree of asymmetry, raising the possibility that small trials showing adverse effects of vitamin D may not have been included in the meta-analysis (*Figure 9*).

Responder analyses

The results of responder analyses for the outcome of the proportion of participants with at least one ARI are presented in *Table 11*. Among participants randomised to the intervention arm of included studies for whom end-study 25(OH)D concentration data were available, no difference in risk of ARI was observed between those who attained a serum 25(OH)D concentration of ≥ 75 nmol/l and those who did not.

TABLE 10 One-step IPD meta-analysis of secondary outcomes, stratified by dosing frequency

Outcome	Bolus dosing					Daily or weekly dosing				
	Number of trials	Proportion with ≥ 1 event subgroup (%)		aOR (95% CI)[a]	*p*-value	Number of trials	Proportion with ≥ 1 event subgroup (%)		aOR (95% CI)[a]	*p*-value
		Control	Intervention				Control	Intervention		
URI	8	606/1052 (57.6)	730/1284 (56.9)	1.03 (0.86 to 1.24)	0.72	11	1050/2234 (47.0)	1077/2449 (44.0)	0.88 (0.78 to 1.00)	0.05
LRI	4	424/1889 (22.4)	427/1922 (22.2)	0.96 (0.82 to 1.13)	0.60	5	118/1396 (8.5)	134/1491 (9.0)	0.98 (0.75 to 1.28)	0.88
Use of antimicrobials for treatment of ARI	4	201/348 (57.8)	203/367 (55.3)	0.79 (0.56 to 1.10)	0.16	5	196/635 (30.9)	210/754 (27.9)	0.87 (0.67 to 1.13)	0.31
Work/school absence as a result of ARI	4	219/409 (53.5)	196/411 (47.7)	0.78 (0.59 to 1.04)	0.10	3	102/223 (45.7)	123/273 (45.1)	1.03 (0.71 to 1.48)	0.88
Severe asthma exacerbation	3	73/343 (21.3)	57/337 (16.9)	0.72 (0.49 to 1.07)	0.11	4	8/140 (5.7)	6/146 (4.1)	0.73 (0.19 to 2.85)	0.65
Severe COPD exacerbation	2	140/207 (67.6)	133/213 (62.4)	0.77 (0.50 to 1.20)	0.25	0	–	–	–	–
Serious adverse event of any cause	10	107/2822 (3.8)	115/3070 (3.8)	1.00 (0.74 to 1.35)	0.99	15	109/2549 (4.3)	106/2783 (3.8)	0.97 (0.73 to 1.30)	0.86
Death as a result of any cause	10	29/2822 (1.0)	35/3070 (1.1)	1.29 (0.71 to 2.35)	0.40	15	19/2549 (0.7)	21/2783 (0.8)	–[b]	–[b]
Death as a result of ARI/respiratory failure	10	4/2797 (0.1)	3/3038 (0.1)	0.61 (0.12 to 3.02)	0.54	15	3/2533 (0.1)	3/2765 (0.1)	–[b]	–[b]
Death as a result of any infection	10	8/2801 (0.3)	5/3040 (0.2)	0.55 (0.17 to 1.80)	0.32	15	7/2537 (0.3)	11/2773 (0.4)	–[b]	–[b]
Hospitalisation or emergency department attendance as a result of ARI	6	4/2081 (0.2)	6/2124 (0.3)	–[b]	–[b]	5	43/1805 (2.4)	34/1862 (1.8)	–[b]	–[b]
Hypercalcaemia	8	8/1062 (0.8)	11/1303 (0.8)	–[b]	–[b]	6	1/677 (0.1)	1/808 (0.1)	–[b]	–[b]
Renal stones	6	0/764 (0.0)	1/1011 (0.1)	–[b]	–[b]	8	4/943 (0.4)	1/1123 (0.1)	–[b]	–[b]

a Adjusted for age, sex and study duration.
b Values could not be estimated as model did not converge.

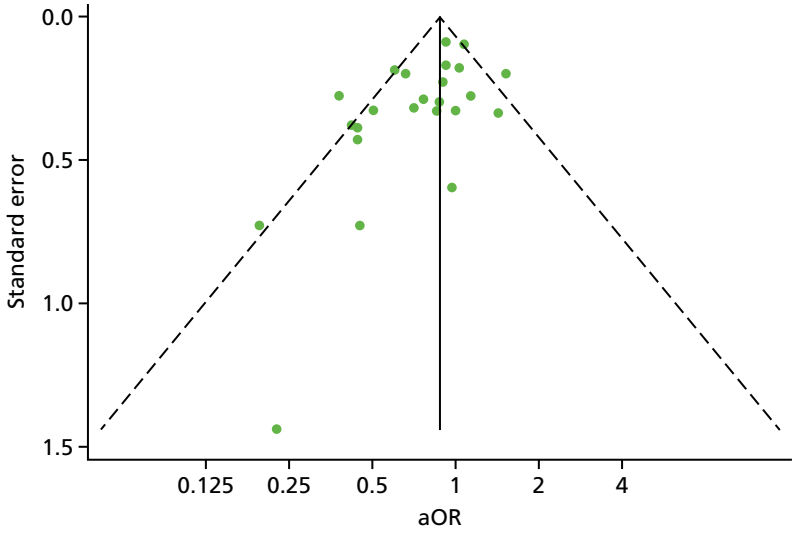

FIGURE 9 Funnel plot with pseudo 95% confidence limits for IPD meta-analysis of proportion of participants experiencing at least one ARI.

TABLE 11 Responder analyses, one-step IPD meta-analysis for the outcome of ARI

25(OH)D status	Number of trials	Impact on ARI	Ratio	*p*-value
		Proportion with ≥ 1 ARI (%)	***aOR (95% CI)***[a]	
Intervention, end-study 25(OH)D level of < 75 nmol/l	18	542/1120 (48.4)	1	–
Intervention, end-study 25(OH)D level of ≥ 75 nmol/l	18	784/1291 (60.7)	0.96 (0.78 to 1.18)	0.68
		Median time (days) to first ARI (IQR)	***aHR (95% CI)***	
Intervention, end-study 25(OH)D level of < 75 nmol/l	11	190 (63, –)[b]	1	–
Intervention, end-study 25(OH)D level of ≥ 75 nmol/l	12	102 (39–312)	1.02 (0.88 to 1.19)	0.76
		Rate of ARI per participant-year	***aIRR (95% CI)***	
Intervention, end-study 25(OH)D level of < 75 nmol/l	18	1.51	1	–
Intervention, end-study 25(OH)D level of ≥ 75 nmol/l	18	2.04	1.01 (0.94 to 1.10)	0.72

IQR, interquartile range.
a Adjusted for age, sex and study duration.
b The 75th percentile for time to first ARI in this group cannot be defined.

Sensitivity analyses

A meta-analysis using IPD of the proportion of participants experiencing at least one ARI, excluding two trials assessed as being at an unclear risk of bias,[55,64] revealed protective effects of vitamin D supplementation consistent with the main analysis (aOR 0.82, 95% CI 0.70 to 0.95; 10,744 participants; $p = 0.01$). Sensitivity analyses for the same outcome, restricted to the 14 trials that investigated ARI as a primary or coprimary outcome, also revealed protective effects of vitamin D supplementation consistent with the main analysis (aOR 0.82, 95% CI 0.68 to 1.00; 5739 participants; $p = 0.05$).

Chapter 5 Discussion

Principal findings

We report the results of the first IPD meta-analysis of RCTs of vitamin D to prevent ARI. In the study population as a whole, vitamin D supplementation reduced the risk of experiencing at least one ARI. Subgroup analysis revealed that daily or weekly vitamin D supplementation without additional bolus doses protected against ARI, while regimens containing large bolus doses did not. Among those receiving daily or weekly vitamin D, protective effects of vitamin D were strongest in individuals with profound vitamin D deficiency at baseline, although those with higher baseline 25(OH)D concentrations also experienced benefit. This evidence was assessed as being of high quality, using the GRADE criteria.[52] As baseline vitamin D status and use of bolus doses varied significantly between studies, our results suggest that the high degree of heterogeneity between trials may be at least partly attributable to these factors. Administration of vitamin D was safe: potential adverse reactions were very rare, and the risk of such events was the same among both participants randomised to intervention arms and those randomised to control arms.

Why might administration of a bolus dose of vitamin D be ineffective for prevention of ARI? One explanation relates to potentially adverse effects of wide fluctuations in circulating 25(OH)D concentrations, which are seen following administration of bolus doses but not with daily or weekly supplementation. Vieth[70] has proposed that high circulating 25(OH)D concentrations following bolus dosing may chronically dysregulate activity of the enzymes responsible for synthesis and degradation of the active vitamin D metabolite 1,25-dihydroxyvitamin D, resulting in decreased concentrations of this metabolite in extrarenal tissues. Such an effect could attenuate the ability of 25(OH)D to support protective immune responses to respiratory pathogens. Increased efficacy of vitamin D supplementation in individuals with lower baseline vitamin D status is more readily explicable, based on the principle that individuals who are the most deficient in a micronutrient will be the most likely to respond to its replacement.

One question raised by our results relates to whether or not vitamin D supplementation will be more beneficial in reducing ARI risk for individuals or for the population as a whole. A targeted approach aimed at individuals would involve testing baseline vitamin D status and offering supplements to those who are deficient. This approach would be likely to result in relatively good adherence (motivation to take a supplement will be higher if an individual knows that they are deficient), but it will be costly and it may not reach a large proportion of the people who stand to benefit. Making additional vitamin D available to the population as a whole in an untargeted fashion (e.g. via food fortification) has some inefficiencies, in that some vitamin D-replete individuals will receive extra vitamin D unnecessarily. However, the strategy also has potential advantages, in that it would provide superior coverage to a 'test-and-treat' approach. The relative merits of the two strategies need to be formally evaluated with a health economic analysis, as suggested in *Future research*.

Our study also investigated the effects of vitamin D supplementation on the risk of acute exacerbations of asthma and COPD. Vitamin D supplementation reduced the rate of asthma exacerbation requiring treatment with systemic corticosteroids overall; non-statistically significant trends towards protection were also seen when the outcome of asthma exacerbation was analysed as the proportion of participants with at least one event and the time to first event. Subgroup analyses for this outcome revealed a trend towards greater protection in participants with a baseline 25(OH)D concentration level of < 25 nmol/l than in those with a higher baseline 25(OH)D concentration level; however, the *p*-value for interaction for this subgroup analysis was 0.25, indicating that we found no statistically significant evidence to implicate baseline vitamin D status as an effect modifier. By contrast, vitamin D supplementation had no statistically significant effect on the risk of COPD exacerbation requiring treatment with antibiotics and/or systemic corticosteroids overall. Subgroup analyses for this outcome revealed a strong protective effect in individuals with baseline 25(OH)D concentrations of < 25 nmol/l, but no

protective effect among individuals with higher baseline 25(OH)D concentration levels. The *p*-value for interaction for this subgroup analysis was 0.003, indicating that baseline vitamin D status modifies the effects of vitamin D supplementation on the risk of COPD exacerbation.

Strengths and limitations

Our study has several strengths. We obtained IPD for all 25 trials identified by our search, the proportion of randomised participants with missing outcome data was small (3.4%), participants with diverse characteristics in multiple settings were represented and 25(OH)D concentration levels were measured using validated assays in laboratories that participated in external quality-assessment schemes. Our findings therefore have a high degree of internal and external validity. Moreover, the subgroup effects we report fulfil published 'credibility criteria' relating to study design, analysis and context.[71] Specifically, the relevant effect modifiers were specified a priori and measured at baseline, *p*-values for interaction remained significant after adjustment for potential confounders and subgroup effects were consistent when analysed as proportions and event rates. Survival analysis revealed consistent trends that did not attain statistical significance, possibly owing to lack of power (fewer studies contributed data to survival analyses than to analyses of proportions and event rates). As discussed above, the concepts that vitamin D supplementation may be (1) more effective when given to those with lower baseline 25(OH)D concentration levels and (2) less effective when bolus doses are administered are also biologically plausible. Although the results are consistent with the hypothesis that baseline vitamin D status and dosing regimen independently modify effects of vitamin D supplementation, we cannot exclude the possible influence of other effect modifiers linked to these two factors. The risk of residual confounding by other effect modifiers is increased for analyses in which relatively few trials are represented within a subgroup, for example when subgroup analyses were stratified by dosing regimen. We therefore suggest caution when interpreting the results in *Tables 6* and *10*.

Our study has some limitations. One explanation for the degree of asymmetry seen in the funnel plot (see *Figure 9*) is that some small trials showing adverse effects of vitamin D may have escaped our attention. With regard to the potential for missing data, we made strenuous efforts to identify published and (at the time) unpublished data, as illustrated by the fact that our meta-analysis includes data from 25 studies, which is 10 more than the largest aggregate data meta-analysis in the field.[24] However, if one or two small trials showing large adverse effects of vitamin D were to emerge, we do not anticipate that they would greatly alter the results of the one-step IPD meta-analysis, as any negative signal from a modest number of additional participants would probably be diluted by the robust protective signal generated from analysis of data from nearly 11,000 participants. A second limitation is that our power to detect effects of vitamin D supplementation was limited for some subgroups [e.g. individuals with baseline 25(OH)D concentration of < 25 nmol/l on bolus dosing regimens] and for some secondary outcomes (e.g. incidence of LRI). Null and borderline significant results for analyses of these outcomes may have arisen as a consequence of type II error. Additional RCTs investigating the effects of vitamin D on the risk of ARI and exacerbation of asthma and COPD are ongoing, and inclusion of data from these studies in future meta-analyses has the potential to increase statistical power to test for subgroup effects. However, all three of the largest such studies for ARI prevention (NCT01169259, ACTRN12611000402943 and ACTRN12613000743763) are being conducted in populations in which profound vitamin D deficiency is rare, and two are using intermittent bolus dosing regimens (ACTRN12611000402943 and ACTRN12613000743763): their results are therefore unlikely to alter our finding of benefit in very deficient individuals, or in those receiving daily or weekly regimens. A third potential limitation relates to the fact that data relating to adherence to study medication were not available for all subjects. However, inclusion of non-adherent participants would bias the results of our intention-to-treat analysis towards the null: thus, we conclude that effects of vitamin D in those who are fully adherent to supplementation will be no less than those reported for the study population overall. Our definition of ARI was wide, incorporating both URI and LRI and, consequently, our overall findings cannot necessarily be generalised to specific ARIs (e.g. those confined to a specific anatomical site or caused by a single pathogen). Finally, we caution that virological, microbiological and/or radiological confirmation was

obtained for a minority of ARI events. ARI is often a clinical diagnosis in practice, however, and, as all studies were double-blind and placebo-controlled, differences in incidence of events between study arms cannot be attributed to observation bias.

Future research

Incorporation of additional IPD from ongoing trials in the field has the potential to increase the statistical power of subgroup analyses; this IPD meta-analysis should therefore be updated when a significant new body of data has accumulated. Given the major impact of ARIs on economic productivity and health-care use, our findings are likely to influence the economic case for the introduction of vitamin D fortification of foods in the UK. Economic models of the cost-effectiveness of vitamin D fortification in the UK should therefore be updated to take account of the previously unappreciated protective effects of vitamin D against ARIs. Such models will need to be populated with accurate data regarding vitamin D intake and the prevalence of vitamin D deficiency in the general population and in subpopulations deemed to be at particular risk of vitamin D deficiency, intake of vitamin D-fortifiable foods and drinks in these populations, attitudes towards different fortification strategies (mandatory vs. voluntary) and the costs of adverse health outcomes such as fractures, falls and ARIs that could be reduced by realising improvements in population vitamin D status. Such modelling would also need to take into account differential profiles of URI compared with LRI in terms of frequency, severity and heath-care costs.

Conclusions

Our synthesis of the current evidence suggests that vitamin D supplementation can prevent ARI, broadly defined. We identified that the greatest potential benefit is for those individuals who are very deficient in vitamin D. Those receiving daily or weekly supplementation without additional bolus doses also experienced particular benefit. Our results add to the body of evidence supporting the introduction of public health measures, such as food fortification, to improve vitamin D status in settings in which profound vitamin D deficiency is common.

Acknowledgements

We thank all the people who participated in the primary RCTs, the teams who performed them and our PPI representatives, Charanjit Patel and Jane Gallagher, for comments on study design and drafts of this manuscript.

Contributions of authors

Adrian R Martineau (Professor of Respiratory Infection and Immunity) led the funding application, assessed the eligibility of studies for inclusion, was directly involved in the acquisition of data for the work, designed statistical analyses in consultation with authors contributing IPD and wrote the first draft of the report.

David A Jolliffe (Postdoctoral Research Fellow) assessed the eligibility of studies for inclusion, designed statistical analyses in consultation with authors contributing IPD and undertook statistical analyses.

Lauren Greenberg (Medical Statistician) designed statistical analyses in consultation with authors contributing IPD and undertook statistical analyses.

John F Aloia (Professor of Medicine), **Peter Bergman** (Associate Professor), **Gal Dubnov-Raz** (Consultant Paediatrician), **Susanna Esposito** (Professor of Paediatrics), **Davaasambuu Ganmaa** (Assistant Professor), **Adit A Ginde** (Professor of Emergency Medicine), **Emma C Goodall** (Assistant Professor), **Cameron C Grant** (Associate Professor), **Wim Janssens** (Professor of Pneumonology), **Megan E Jensen** (Postdoctoral Clinical Researcher), **Conor P Kerley** (Postdoctoral Clinical Researcher), **Ilkka Laaksi** (Chief Administrative Medical Officer), **Semira Manaseki-Holland** (Senior Clinical Lecturer), **David Mauger** (Professor of Public Health Sciences and Statistics), **David R Murdoch** (Professor of Pathology), **Rachel Neale** (Associate Professor), **Judy R Rees** (Assistant Professor), **Steve Simpson Jr** (Postdoctoral Research Fellow), **Iwona Stelmach** (Professor of Paediatric Allergy), **Geeta Trilok Kumar** (Associate Professor) and **Mitsuyoshi Urashima** (Professor of Molecular Epidemiology) were all directly involved in the acquisition of data for the work.

Carlos A Camargo Jr (Professor of Emergency Medicine, Medicine and Epidemiology) was a co-applicant in the funding application, assessed the eligibility of studies for inclusion and was directly involved in the acquisition of data for the work.

Christopher J Griffiths (Professor of Primary Care) was a co-applicant in the funding application and was directly involved in the acquisition of data for the work.

Richard L Hooper (Reader in Medical Statistics) assisted in the funding application, designed statistical analyses in consultation with authors contributing IPD and undertook statistical analyses.

All authors critically revised the manuscript for important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Publications

Jolliffe DA, Greenberg L, Hooper RL, Griffiths CJ, Camargo CA, Kerley CP, *et al.* Vitamin D supplementation to prevent asthma exacerbations: a systematic review and meta-analysis of individual participant data. *Lancet Respir Med* 2017;**5**:881–90.

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

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Appendix 1 Electronic search strategy

The full electronic search strategy for MEDLINE is presented.

Cochrane highly sensitive search strategy for identifying randomised controlled trials

#1. randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]

#2. animals [mh] NOT humans [mh]

#3. #1 NOT #2

Terms specific to vitamin D

#4. Vitamin D OR vitamin D2 OR vitamin D3 OR cholecalciferol OR ergocalciferol OR alphacalcidol OR alfacalcidol OR calcitriol OR paricalcitol OR doxerocalciferol

Terms specific to acute respiratory infection

#5. Acute Respiratory Infection OR Upper Respiratory Infection OR Lower Respiratory Infection OR Respiratory Tract Infection OR Common Cold OR Sinusitis OR Pharyngitis OR Laryngitis OR Laryngotracheobronchitis OR Tonsillitis OR peritonsillar abscess OR Croup OR Epiglottitis OR supraglottitis OR Otitis Media OR Pneumonia OR Bronchopneumonia OR Bronchitis OR Pleurisy OR Pleuritis

Terms specific to asthma

#6 Asthma OR bronchial hyperreactivity OR bronchial hyper-reactivity OR respiratory hypersensitivity OR reactive airway

Terms specific to chronic obstructive pulmonary disease

#7 Chronic obstructive pulmonary disease OR COPD OR COAD OR emphysema OR chronic bronchitis OR AECB OR AECOPD

Combination of terms to identify randomised controlled trials of vitamin D for the prevention of acute respiratory infection

#3 AND #4 AND #5

Combination of terms to identify randomised controlled trials of vitamin D conducted in patients with asthma

#3 AND #4 AND #6

Combination of terms to identify randomised controlled trials of vitamin D conducted in patients with chronic obstructive pulmonary disease

#3 AND #4 AND #7

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HTA
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